Modulation of spontaneous and volitional swallowing: Methodological and behavioural analyses

A Thesis Submitted in Partial Fulfilment of the Requirements
for the Degree of Doctor of Philosophy

Kristin M. Lamvik

Department of Communication Disorders
The University of Canterbury, Christchurch, New Zealand
February 2016

Abstract

This research programme was inspired by a desire to understand the neural underpinnings of an interesting patient cohort with an atypical presentation of dysphagia (Huckabee, Lamvik, & Jones, 2014). These patients presented with mis-sequenced, rather than weakened, pharyngeal constriction when swallowing. As a result, they were unable to coordinate streamlined food or liquid transfer from the pharynx into the oesophagus. This cohort gave rise to a series of studies to explore the nature of underlying neural control of swallowing and mis-swallowing, behavioural modulation of volitional and spontaneous swallowing, and methodological limitations of existing diagnostic techniques.

A prospective incidence study is currently ongoing to identify specific patient groups who exhibit pharyngeal mis-sequencing and to further explore mechanisms of pharyngeal sequencing itself. This study is evaluating swallowing in patients with dysphagia as a sequela of four brain disorders (n = 100): base of skull surgery, brainstem stroke, cortical stroke and Parkinson's disease. Manofluoroscopic results from current participants (n = 7) are reported in this thesis. Completion of this project will likely translate immediately to improved patient care and greater scientific understanding of the complex neural control of swallowing.

Previous research has documented that pressure and duration of brainstem-generated pharyngeal swallowing can be cortically modulated (Bülow et al., 2001; Fukuoka et al., 2013; Wheeler-Hegland et al., 2008; Witte et al., 2008). But there is a commonly held belief that the sequence of pharyngeal pressure remains constant (Ertekin, 2011). Intensive training was provided to healthy adults (n = 6) to determine if participants can volitionally alter latency of pharyngeal closure, thereby evaluating the capacity for pharyngeal adaptation in a healthy system. Following training, participants were able to reduce temporal separation of peak pressure between the proximal and distal pharyngeal sensors from a baseline median of 188 ms (interquartile range (IQR) = 231 ms) to 68 ms (IQR = 92 ms; $p = 0.002$). However, there was a contemporaneous reduction in swallowing duration post-training ($p = 0.03$). Participants may have achieved a reduced peak-to-peak latency through optimizing a reduction in overall swallowing duration, suggesting volitional modulation cannot alter the reflexive pharyngeal sequence to a pathologic level.

Sleep has been associated with periods of relative cortical quiescence (Orr, Johnson, & Robinson, 1984), enabling evaluation of volitional and automatic swallowing conditions. Pharyngeal swallowing was analysed with low and high-resolution manometry in healthy participants (n = 20) and patients with dysphagia (n = 3). Results indicated sleep swallows were of lower amplitude than supine awake swallows ($p < 0.01$), with no significant difference between awake and supine swallows in terms of latency ($p = 0.11$) or slope ($p = 0.73$). This contrasts to findings of patients with dysphagia, who presented with a clear pattern of mis-sequenced pressure during sleep, even in the two patients who were able to sequence pressure adequately to enable functional swallowing when awake. This may provide additional data regarding the debate or the role of volition and arousal in swallowing motor control.

Advancements in circumferential sensor technology now enable comparison of manometric catheters with similar diameter (2.1 mm unidirectional diameter to 2.75 mm circumferential diameter). Understanding differences in measurement between these two intraluminal pressure measurement devices is critical to explain the variability in normative data collected by similar intraluminal instruments. A comparison of low- and high-resolution manometry found significant differences in measurement of temporal and amplitude characteristics. Further, in-vivo and in-vitro studies were completed with low- and high-resolution manometry, with stable measurement in low-resolution manometry contrasting to unstable high-resolution manometry measurement, varying both between studies ($p < 0.01$) and within sensors ($p < 0.01$). Further, this measurement error is not corrected via the standard operating instructions.

Topical nasal anaesthetic is used in research and clinical examinations with pharyngeal high-resolution manometry and recommended in clinical protocols (Knigge, Thibeault, & McCulloch, 2013). However, it is unclear if desensitizing the nasal mucosa improves procedure tolerability or affects pharyngeal swallowing. Results indicate topical nasal anaesthetic provides no improvement in procedure comfort ($p = 0.23$), with potential alterations in pharyngeal swallowing as compared to placebo conditions. Lastly, Knigge et al. (2014) provide the only published clinical protocol for analysis of high-resolution manometry spatiotemporal plots using existing system-based technologies (e.g., ManoScan™ high-

resolution manometry systems). Results indicate that, following training, intra-rater reliability was 0.99 (range = 0.97 – 1.0; SD = 0.01) while inter-rater reliability was variable across measures (range = 0.11-0.95; SD=0.32). While this will likely have an impact on current best practice, further research is needed to standardize measurement of pharyngeal swallowing using high-resolution manometry. The studies included in this programme of research contribute to shortcomings in the literature regarding best practice in diagnostic methodology and the nature of underlying neural control of pharyngeal swallowing.

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Please detail the nature and extent (%) of contribution by the candidate:

The project was conceived jointly between the candidate and the primary supervisor; the candidate collected and analysed data, and wrote the manuscript under the supervision of the co-authors.

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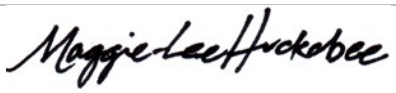
Name: *Maggie-Lee Huckabee PhD* Signature:  Date: *26.02.16*

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Chapter 12: Characterisation and Correction of Measurement Error in Low and High-resolution Manometry: In-Vitro and In-Vivo

Lamvik, K., Guiu-Hernandez, E., Jones, R., Huckabee, M-L. (in press). Characterization and correction of pressure drift in the ManoScan™ high-resolution manometry system: In-vitro and in-vivo. *Neurogastroenterology and Motility*. doi: 10.1111/nmo.12770

Please detail the nature and extent (%) of contribution by the candidate:

The project was conceptualised largely by the Candidate, supported by the supervisory team. The candidate collected (70%) and analysed the data (50%) with Esther Guiu-Hernandez and co-wrote the manuscript (80%) with Esther Guiu-Hernandez, under the supervision and with input from the co-authors.

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Name: *Maggie-Lee Huckabee PhD* Signature: Maggie-Lee Huckabee Date: *26.02.16*

Acknowledgements

First and foremost, I wish to thank my supervisors for their tremendous support of my doctoral research. I have grown both personally and professionally under the supervision of this great team. Prof Maggie-Lee Huckabee inspired my pursuit of a doctoral degree and has supported me wholeheartedly during these past three years. She has become not only my mentor, but a great friend. I am so thankful for the robust number of experiences Prof Huckabee has provided me with above and beyond day-to-day research, including guest lecturing, trips to collaborating research and medical centres and presentations at national and international conferences. I am constantly impressed by the passion to which Prof Huckabee instils in her research and I thank her for helping me become a more astute thinker and caring clinician. As well, Prof Richard Jones has been a continued source of knowledge and expertise. He has contributed greatly to our work these past three years and has been a reliable source of insight and friendly advice. It is his expert eye for detail and novel perspective on our research that has been so invaluable in this successful team effort. I would like to thank him for being such a kind a receptive supervisor, not to mention neighbour! I would also like to extend my gratitude to my supervisory committee, including Prof Art Miller and Mr Phil Bird.

I am deeply appreciative of the contribution by Esther Guiu-Hernandez, a biomedical engineer who has provided deep knowledge of engineering, data management and analysis vital in completion of numerous studies in this work. But above and beyond her technical skillsets, Esther has provided a warm and ever-present support that I turned to frequently for reassurance. I thank her for her availability in collaborating to solve problems both small and large and for sharing this journey with me as a life-long friend.

I am very grateful to the patients and participants who enabled the completion of the studies within this research programme. We implemented procedures that are considered invasive to some. Yet, their agreeable nature and willingness to contribute to science will always be remembered. Specifically, I would like to personally acknowledge Eric, Rosie and Heine - testaments to the strength of the human spirit, inspiring me continually with their motivation to overcome any obstacle they face. Knowing them has been an honour.

To my fellow students at the University of Canterbury Department of Communication Disorders and specifically the Rose Centre for Stroke Recovery and Research, I thank you deeply for your support and friendship over the last three years. You have provided me with a sounding board for not only questions arising from the work we complete, but also the concerns we all share as emerging researchers. I wish to send a warm appreciation to Sarah Davies, Molly Kallesen, Olivia Apperley, Sonja Sauer, Karen Ng, Kerstin Erfmann and the entirety of the ever-evolving group of proficient, bright and warm hearted students of the Rose Centre. It has been an honour working and studying with you all. Further, I would like to send great thanks to Dr Phoebe Macrae, an exemplary researcher and mentor. We are terrifically lucky to have your insights and good humour at the Rose Centre and I thank you for the time and advice you have provided me. Lastly, Sara Moore and Fiona Bellett deserve heartfelt thanks as colleagues who never fail to put a smile on my face.

I would like to acknowledge financial support from the New Zealand Neurological Foundation, Canterbury Medical Research Foundation and the New Zealand Brain Research Institute Doctoral Scholarship, enabling not only pursuit of this degree but also research and travel that made my experience robust. Further, I wish to acknowledge the Canterbury District Health Board, specifically Dr John Fink and the Speech Language Therapy team, for their support in projects both completed and ongoing. This extends to Valerie Lim, Deirdre Tay and Melissa Ling at Singapore General Hospital. It is with great hope our collaboration will begin to prosper future in regards to recruitment and data collection. I would also like to extend my gratitude to Prof Stephanie Stokes and Dr Kathryn Mackinven, who provided high-quality feedback and support in the submission of countless grant applications.

I wish to send my deepest thanks to my family, old and new, near and far. To my parents, brothers Robby and Ryan, sister Kate and her growing family, thank you for always being just a phone call away. Your support is never-ending, even though we live a world apart. Lastly, the unfailing support, advice and encouragement of my partner (and husband-to-be) Szymon has helped me become who I am today. Having him by my side is a true gift. Plus, the laughs, hugs and positivity given by his son, Hugo, never fail to put a smile on my face. Their well wishes and, at times, much needed distractions, have been the fuel needed to support my doctoral pursuits. It is with great pride that I begin the next steps of my life with them by my side.

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Preface

This PhD thesis conforms to the referencing style recommended by the American Psychological Association Publication Manual (6th ed.) and spelling recommended by the Oxford Dictionary (http://oxforddictionaries.com). The research for this PhD thesis was carried out between February 2013 to February 2016, while the candidate was enrolled in the Department of Communication Disorders at the University of Canterbury. The research was based at the New Zealand Brain Research Institute until December 2014, after which the research was based at the UC Rose Centre for Stroke Recovery and Research. Prof Maggie-Lee Huckabee and Prof Richard Jones supervised this research, along with supervisory committee Prof Art Miller and Mr Phil Bird. The research was conducted with support from the New Zealand Brain Research International Doctoral Scholarship.

Conference Presentations

- Biomouth Symposium (Dunedin, New Zealand, 2013)
- UC Postgraduate Showcase (2013, Christchurch, New Zealand) – awarded 1st place in PhD Category and joint winner as Overall Presenter
- Health Research Society Grand Round Series (2014, Christchurch, New Zealand)
- 22nd Annual Meeting of the Dysphagia Research Society (2014; Nashville, TN, USA)
- 4th Congress, European Society for Swallowing Disorders (2014, Brussels, Belgium)
- New Zealand Physicists & Engineers in Medicine Conference (2014, Christchurch, New Zealand)
- Stroke Rehab: From No-Tech to Go-Tech Conference (2015, Christchurch, New Zealand) – awarded Best Student Presentation (platform presentation)
- 5th Congress of the European Society for Swallowing Disorders (2015, Barcelona, Spain)
- 23rd Annual Meeting of the Dysphagia Research Society (2016, Tucson, AZ, USA)

The following publications were generated during this PhD Research (with two additional papers under review):

Journal Articles

Lamvik, K., Guiu-Hernandez, E., Jones, R., Huckabee, M-L. (in press). Characterization and correction of pressure drift in the ManoScan™ high-resolution manometry system: In-vitro and in-vivo. *Neurogastroenterology and Motility*. doi: 10.1111/nmo.12770

Lamvik, K., Huckabee, M-L. (2015). The Rose Centre for Stroke Recovery and Research: Harnessing Biotechnology in Rehabilitation and Research. *EP Lab Digest*, 15(2), 17-19.

Lamvik, K., Jones, R., Huckabee, M-L. (2015). The capacity for volitional control of pharyngeal swallowing in healthy adults. *Physiology and Behaviour*, 1(152): 257-63. doi: 10.1016/j.physbeh.2015.09.026.

Lamvik, K., Macrae, P., Doeltgen, S., Collings, A., Huckabee, M-L. (2014). Normative data for pharyngeal pressure generation during saliva, bolus and effortful saliva swallowing across age and gender. *Speech, Language and Hearing*. 17(4), 210-215. doi: 10.1179/2050572814Y.0000000042

Huckabee, M-L, **Lamvik, K.,** Jones, R. (2014). Pharyngeal mis-sequencing in dysphagia: Characteristics, rehabilitative response, and etiological speculation. *Journal of the Neurological Sciences*. 343 (2014), 153-158. doi: 10.1016/j.jns.2014.05.064

Published Abstracts

Lamvik, K., Erfmann, K., Jones, R., Huckabee, M-L. (2014). Sequencing of pharyngeal pressure during wake and sleep swallowing. *New Zealand Medical Journal*. 127(1396).

Guiu, E., **Lamvik, K.**, Jones, R., Huckabee, M-L. (2014). Measurement consistency of high-resolution manometry. *Australasian Physical & Engineering Sciences in Medicine*, 38: 185-186.

List of Abbreviations

AIM	automated impedance manometry
ANOVA	analysis of variance
CN	cranial nerve
CNS	central nervous system
CT	computed tomography
CPA	cerebellopontine angle
CPG	central pattern generator
EEG	electroencephalography/electroencephalogram
EMG	electromyography/electromyogram
fMRI	functional magnetic resonance imaging
fNIRS	functional near-infrared spectroscopy
HRM	high-resolution manometry
ICC	intraclass correlation coefficient
ITC	interpolated thermal compensation
IQR	interquartile range
LES	lower oesophageal sphincter
MEG	magnetoencephalography/magnetoencephalogram
MRI	magnetic resonance imaging
NA	nucleus ambiguous
NREM	non-rapid eye movement
NTS	nucleus tractus solitaries
PD	Parkinson's disease
PEG	percutaneous endoscopic gastrostomy
REM	rapid eye movement
sEMG	surface electromyography
SRI	swallow risk index
TC	thermal compensation
TMS	transcranial magnetic stimulation
TNA	topical nasal anaesthetic
UES	upper oesophageal sphincter
VEES	videoendoscopic examination of swallowing
VFSS	videofluoroscopic swallowing study

PART I: INTRODUCTION

Chapter 1: Introduction

This research programme was inspired by a desire to understand the neural underpinnings of an interesting patient cohort with an atypical presentation of dysphagia (Huckabee et al., 2014). These patients present with mis-sequenced, rather than weakened, pharyngeal constriction when swallowing. As a result, they were unable to coordinate streamlined food or liquid transfer from the pharynx into the oesophagus. This pharyngeal mis-sequencing contributed to aspiration, nasal redirection and, for some, a considerable inability to safely tolerate a diet by mouth. The incidence and natural history of pharyngeal mis-sequencing in patients with dysphagia is not yet known, as pharyngeal mis-sequencing itself is not easily observable on the current gold standard, videofluoroscopic swallowing study (VFSS), due to inadequate temporal resolution. Pharyngeal mis-sequencing is, however, readily detected using manometry. The original purpose of this programme of research was to initiate a longitudinal, manofluoroscopic evaluation of a broad neurogenic population (n = 100) to identify the prevalence and characterize the pathophysiology of this dysphagic presentation. While data collection for this study exceeds the scope of this thesis and is ongoing, preliminary results are discussed in Chapter 7. Importantly, this work has given rise to a series of adjunctive studies to further explore mechanisms of pharyngeal mis-sequencing and the nature of underlying neural control of swallowing. This work constitutes the bulk of this thesis.

The aetiology of mis-sequencing requires definition. It is unclear if this atypical swallowing impairment is (i) a primary feature of the neurological deficit itself or (ii) a maladaptive compensatory response as a consequence of chronic dysphagia. This question is targeted in Part II of this thesis, which explores behavioural modulation of volitional and spontaneous swallowing. Although historically it has been accepted that the pharyngeal phase of swallowing is a patterned reflex (Ertekin, 2011), recent evidence suggests that pharyngeal swallowing can be under greater volitional control than previously thought (Babaei et al., 2013; Hamdy, Aziz, Thompson, & Rothwell, 2001; Huckabee, Deecke, Cannito, Gould, & Mayr, 2003). Therefore, a fundamental question emerges: do humans possess the capability to volitionally alter discrete sequential elements of the overall motor plan of the pharyngeal phase of swallowing and, if so, to what extent? If not, it would follow that mis-sequencing is likely a characteristic of the underlying neurological deficit. Chapter 8 summarizes a study

that investigates whether healthy participants can modulate temporal characteristics of pharyngeal pressure upon completion of an intensive training protocol using pharyngeal manometry as visual biofeedback. In essence, the study evaluated the capacity of healthy participants to replicate the presentation of the patient cohort with pharyngeal mis-sequencing (Huckabee et al., 2014).

The abovementioned study explores the potential for maladaptive alteration to pharyngeal swallowing in the mis-sequencing cohort. However, mis-sequencing in the patient cohort could be driven by an inhibition of cortical input to the motor plan as a result of neurologic impairment. As most patients in the mis-sequencing cohort did not present with direct damage to the medullary swallowing centre, it is surprising that the basic motor-sequence of pharyngeal swallowing was impaired (Huckabee et al., 2014). The question arose whether simultaneous pharyngeal pressure generation is characteristic of basic, reflexive pharyngeal swallowing and if the superior to inferior pattern is present only in volitional prandial ingestion (Huckabee et al., 2014). Thus, in neurological patients presenting with pharyngeal mis-sequencing, this capability may be lost. Our current understanding of central representation of swallowing may be inadequate to account for the complexities in human deglutition. Therefore, the primary investigators evaluated a patient cohort with mis-sequencing (n = 3; Chapter 7) and a healthy cohort (n = 20; Chapter 9) during sleep to further characterize the pharyngeal swallowing response when volitional modulation is reduced. Published literature reports frequency of swallowing during sleep (Sato et al., 2006) and limited physiologic details, such as swallowing respiratory coordination (Pohl et al., 2013), but there are no reports of amplitude and temporal characteristics of pharyngeal pressure generation in sleep. Changes in pharyngeal pressure measures when asleep, as compared to when awake, may help elucidate the role of the cortex in modulating the pharyngeal swallowing response.

During execution of the behavioural studies in Part II, it quickly became apparent that existing diagnostic methods might be inadequate for understanding the rapid sensorimotor swallowing response. Current best practice in evaluation of dysphagia relies heavily on the use of VFSS, which provides clear visualization of bolus flow and biomechanics. However, when basing assessment on subjective analysis of two-dimensional movement, clinicians may be inappropriately inferring function without objective testing of timing and amplitude of pharyngeal pressure at greater temporal resolutions. Other techniques such as conventional

low-resolution manometry are not commonly utilized in clinical practice and recent advancements with the development of high-resolution manometry (HRM) have not been evaluated in terms of reliability and validity. Further, notable measurement error and uncertainty in optimal analysis methods for pharyngeal HRM were observed experimentally in Part II of this research programme, but are rarely discussed in the literature (Robertson et al., 2012). Therefore, Part III of this work contains methodological analyses investigating the reliability, validity and measurement accuracy of both low- and high-resolution pharyngeal manometry.

Chapter 11 summarizes a within-subject comparison of low- and high-resolution manometry, as discrepancies in normative data have been evidenced between these two intraluminal pressure measurement devices. Following this, a detailed analysis of instrument performance and measurement error is described with regard to low- and high-resolution manometry (Chapter 12). This is followed by a practical study delineating the effects of topical nasal anaesthetic application with HRM (Chapter 13) and reliability of clinical swallowing measurements performed by Speech-Language Pathologists using HRM (Chapter 14). The studies summarized in Part III are paramount in understanding possible methodological strengths and weaknesses of manometry to guide best practice for the selection and use of this instrumentation.

The present research programme provides directives for increasing and refining the use of more sensitive and robust instrumental techniques, such as pharyngeal manometry or manofluoroscopy, in comprehensive clinical evaluations of dysphagia. Greater specificity in the evaluation of swallowing can increase confidence in differential diagnosis, such as identifying patients with pharyngeal mis-sequencing from those with reduced pharyngeal motility. This is critical, as risk of negative secondary outcomes, such as aspiration pneumonia, death and increased costs of care, are compounded should clinicians fail to identify or misdiagnose the swallowing impairment. The studies included in this programme of research contribute to shortcomings in the literature regarding volitional modulation and the nature of underlying neural control of pharyngeal swallowing. The act of deglutition is highly complex and greater specificity is paramount, not only in diagnosis but in broader understanding of swallowing neurophysiology, for the advancement of best practice in this field.

Chapter 2: Central Control of Swallowing

Swallowing is controlled by the central nervous system (CNS) through a functional interplay between infra- and supra-tentorial structures. Lasting 0.6 – 1.0 s, safe and efficient swallowing is reliant on an accurate and timely cascade of sensorimotor responses (Jean, 2001; Lang, 2009). Detailed animal studies have provided a robust foundation for current understanding of swallowing neural control (Amri, Car, & Jean, 1984; Car, Jean, & Roman, 1975; Doty & Bosma, 1956; Jean, Car, & Roman, 1975). However, with advancements in imaging technologies, this understanding is quickly evolving. This review will commence with peripheral control mechanisms, largely constituted of cranial nerves (CN) and then focus on central control mechanisms, including the brainstem and higher cortical structures.

2.1 Peripheral control of swallowing

Of the twelve cranial nerves, eight have direct or indirect relationships with swallowing sensorimotor control in the CNS. The most rostral cranial nerves, olfactory (CN I) and optic (CN II), terminate in the cerebrum and the trigeminal (CN V), facial (CN VII), glossopharyngeal (CN IX), vagus (CN X), spinal accessory (CN XII) and hypoglossal (CN XII) nerves arise from the pons and medulla in the brainstem (Jacobson & Marcus, 2011). The five most prominent swallowing-related cranial nerves are discussed in detail below.

The trigeminal nerve (CN V), the largest cranial nerve, is a mixed sensory and motor cranial nerve, with motor nerves arising from the pons and sensory nerves terminating in the pons (Jean, Amri, & Calas, 1983). This nerve is split into three branches, namely the ophthalmic branch, maxillary branch and the mandibular branch. Relevant to swallowing, the maxillary branch transmits sensory input from the skin of the maxilla, upper lip, upper teeth, nasal mucosa, sinuses and palate (Scott, 2014). The largest branch, the mandibular, is the only branch serving motor and sensory functions. This branch relays sensory information from the skin over the chin, lower lip, lower teeth, jaw, skin over the cheek, inside the oral cavity and sensation from the anterior two-thirds of the tongue (Scott, 2014). With regards to motor function, this nerve innervates the muscles of mastication, including the temporalis, masseter, lateral and medial pterygoids, mylohyoid, anterior belly of the digastric, tensor veli palatini and tensor tympani muscles (Jacobson & Marcus, 2011). The mylohyoid and anterior belly of the digastric muscles are critical for jaw opening and hyolaryngeal excursion. Impairment of

this cranial nerve can impact not only mastication, but hyolaryngeal complex movement, with secondary consequences for epiglottic deflection and upper oesophageal sphincter (UES) opening. Impairment in the trigeminal nerve can also cause sensory disturbances in anterior bolus awareness (Scott, 2014). Evaluation of this cranial nerve involves testing symmetry of touch sensation, as well as tone and function of muscles involved in mastication.

The facial nerve (CN VII) is a mixed sensory and motor cranial nerve with motor nuclei also arising from the pons and sensory nuclei housed in the NTS (Sherwood, 2005). This nerve controls the muscles of facial expression and provides general taste sensation for the anterior two-thirds of the tongue. Relevant to swallowing, CN VII innervates the buccinators, zygomaticus, orbicularis oris, risorius, stylohyoid and posterior belly of the digastric (Campbell, 2015). Relaxation of the orbicularis oris allows for mouth opening during oral feeding, with activation of accessory facial muscles above as needed to accommodate larger bolus types (Ertekin et al., 2013). The stylohyoid and posterior belly of the digastric aid in moving the tongue base superiorly and posteriorly, useful in oral containment of a bolus and subsequent pharyngeal bolus transfer. The motor fibres of the chorda tympani branch innervate the submandibular and sublingual salivary glands, mucous membranes of the nasopharynx and palate (Scott, 2014). Lastly, the sensory component provides taste sensation for the anterior two-thirds of the tongue, in conjunction with the other cranial nerves involved in taste processing (Scott, 2014). Impairment in facial nerve functioning can lead to paresis or paralysis of the muscles of the face (predominantly lower facial muscles due to bilateral innervation of the upper face) resulting in poor oral bolus containment, abnormal secretion production and/or reduced or absent taste from the anterior tongue (Scott, 2014). Testing for this cranial nerve can be completed by inspection of facial movement, inspection of salivary function (in conjunction with CN IX) and taste recognition on the anterior two-thirds of the tongue.

The glossopharyngeal nerve (CN IX) is a mixed sensory-motor nerve exiting bilaterally at the jugular foramen. The sensory nuclei is located in the nucleus tractus solitarius (NTS) in the medulla, with the primary motor nuclei in the NA (Steele & Miller, 2010). The motor component provides innervation to the stylopharyngeus muscle as well as glands in the pharynx and larynx, including the parotid gland (Campbell, 2015). With regard to sensation, this cranial nerve provides tactile information from the upper pharynx and tonsil, posterior

one-third of tongue and provides taste information from the posterior one-third of the tongue (Scott, 2014). As this cranial nerve travels closely to the vagus nerve, select fibres from CN IX and X are referred to as the pharyngeal plexus, responsible for innervation of critical swallowing musculature including the palatoglossus, glossopharyngeus, levator veli palatini, palatopharyngeus, pharyngeal constrictors and salpingopharyngeus. Of note, however, both CN IX and CN X have fibres that function independently of the pharyngeal plexus. Testing of CN IX is largely completed in conjunction with CN X. For example, when testing the gag reflex, the afferent sensory fibres arise from the glossopharyngeal nerve, while the motor response of this reflex is innervated by the vagus nerve. Therefore, it can be difficult to distinguish a specific impairment of the glossopharyngeal nerve from a clinically reduced gag response. Loss of function to the glossopharyngeal nerve alone is uncommon (Scott, 2014).

The vagus nerve (CN X) is the longest cranial nerve, controlling smooth, skeletal and cardiac muscles from the head and neck to the abdomen. It provides sensory and motor information from the pharynx and larynx, which are responsible for production of voice and cough responses. Like CN IX, the sensory nuclei are located in the NTS, while the primary motor nuclei are in the nucleus ambiguous (NA) in the medulla (Campbell, 2015) The vagus innervates the pharynx and larynx through three primary branches: the pharyngeal nerve, superior laryngeal nerve and the recurrent laryngeal nerve. The pharyngeal nerve forms the pharyngeal plexus with fibres from CN IX, innervating critical pharyngeal musculature such as the superior, middle and inferior pharyngeal constrictors (Campbell, 2015). The superior laryngeal nerve provides innervation to the tonically contracted cricopharyngeus muscle, as well as laryngeal sensory information and innervation to the cricothyroid (Jones, Hammer, Hoffman, & McCulloch, 2014). The recurrent laryngeal nerve enables movement (both abduction and adduction) of the vocal cords through innervation of the posterior and lateral cricoarytenoids, thyroarytenoids and interarytenoids (Campbell, 2015; Scott, 2014). The vagus nerve and fibres contributing to the pharyngeal plexus provide general sensation to the pharynx, larynx, oesophagus, as well as taste sensation from the epiglottic region (Scott, 2014). Relevant to the present work, damage to the vagus nerve can cause severe impairment in swallowing sensorimotor control and airway protection. In addition to impaired phonation as a result of paresis or paralysis of laryngeal musculature, impairments with the vagus nerve can result in reduced cough sensation or integrity of motor reaction in response to aspiration and impairments in palatal and pharyngeal tone and motility. Independent CN X testing

entails assessment of vocal quality, integrity of cough response and response to inhalation of an irritant, such as citric acid (Miles, Zeng, McLauchlan, & Huckabee, 2013). With CN IX, clinicians can evaluate the pharyngeal plexus by investigating symmetry and motility of the palate and gag reflex (Campbell, 2015).

The hypoglossal nerve (XII) is a motor-only nerve supplying all of the intrinsic and most of extrinsic muscles of the tongue (Felton, Gaige, Reese, Wedeen, & Gilbert, 2007; Gilbert, Daftary, Campbell, & Weisskoff, 1998). The intrinsic muscles of the tongue (namely the verticalis, transverse and longitudinal) alter the length, width and curvature of the tongue. The extrinsic lingual muscles – the genioglossus, hyoglossus and styloglossus – aid in protrusion and retraction of the tongue and tongue root (Campbell, 2015; Felton et al., 2007). The hypoglossal nerve also innervates the geniohyoid muscle in conjunction with cervical spinal nerves 1 and 2, termed ansa cervicalis (Dodds, Stewart, & Logeman, 1990). The geniohyoid muscle contributes to the the submental muscle group together with the mylohyoid and anterior belly of the digastric innervated by CN V. Unilateral or bilateral damage can lead to lingual weakness, deviation and fasciculations, impairing not only speech, but bolus formation and preparation for ingestion and may contribute to reduced anterior hyoid movement. This nerve can be indirectly tested through evaluation of tone and function of the tongue at rest and with movement.

2.2 Brainstem control of swallowing

The brainstem plays a critical role in swallowing neural control. A normal human foetus can swallow by the 12th gestational week, prior to the development of cortical and subcortical structures (Jean, 2001; Thexton, 1992). The complex, but stereotyped, swallowing response is controlled by a medullary central pattern generator (CPG). This is based on animal studies, where patterned and replicable timing of the pharyngeal swallow was evoked using electrical current applied directly to brain structures, even in decerebrate animals (Amri et al., 1984; Dick, Oku, Romaniuk, & Cherniack, 1993; Doty, 1951; Ertekin & Aydogdu, 2003; Jean, Amri, & Calas, 1983; Jean, 2001; Miller, 2002). The CPG can be thought of as a functionally connected pools of neurons capable of producing a rhythmic, predictable output in the absence of afferent sensory input (Harris-Warrick, 2010). Said differently, a CPG is “an ensemble of neural elements whose properties and connectivity can give rise to characteristic patterns of rhythmic activity in absence of external feedback” (Rossignol & Dubuc, 1994).

CPGs are found in other systems as well, such as mastication (Morquette et al., 2012), locomotion (Guertin & Steuer, 2009) and respiration (Abdala et al., 2009). In fitting with its definition, the output of the swallowing CPG creates a fairly invariant, 'reflexive' response with a constant sequence of motor events (Jean, 2001; Miller, 2008). The swallowing CPG can be parsed into dorsal and ventral elements, functionally connected by interneurons and cranial nerve cell bodies in the NTS and the NA, respectively (Jean, 2001). As shown in Figure 2.1, adequate function of the swallowing-CPG is dependent on afferent and efferent transmission from the swallowing-related cranial nerves bilaterally represented in the CNS (Miller, 2008). Many components of the swallowing network are not dedicated to swallowing alone but can also serve other central networks. Therefore, the patterned swallowing response is completed in close conjunction with coordination of associated functions, such as respiration and mastication, through shared pools of interneurons (Jean, 2001).

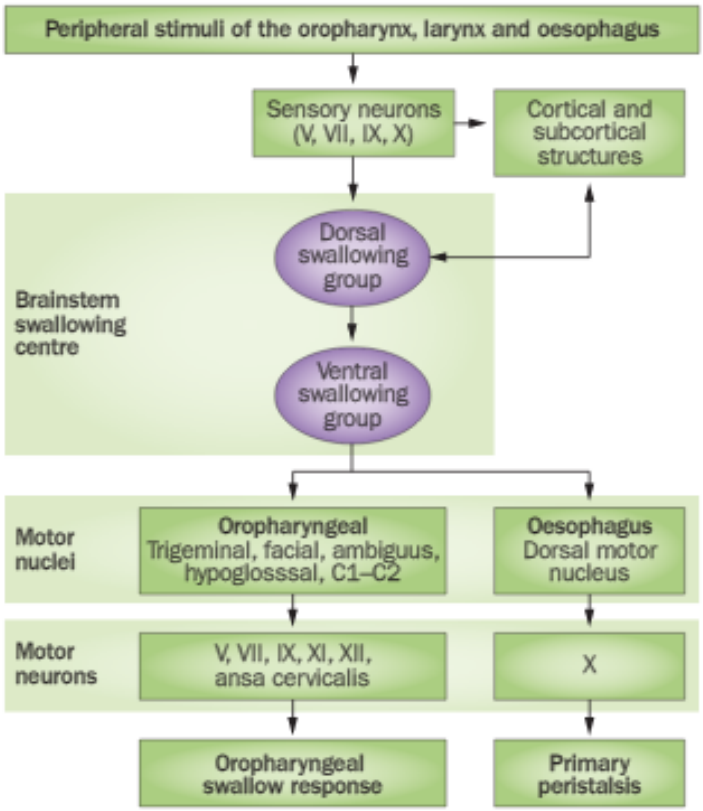


Figure 2.1 Flow chart summarizing the pathway of afferent transmission from peripheral input to elicit a motor swallowing response (Clavé et al., 2016).[1] Note the complexity in the oropharyngeal response as compared to oesophageal peristalsis.

[1] Reprinted with permission from Macmillan Publishers Ltd. Clavé, P., & Shaker, R. (2015). Dysphagia: current reality and scope of the problem. Nature Reviews. Gastroenterology & Hepatology, 12(5), 259–70), copyright (2016).

As the main afferent structure, the NTS in the dorsal medulla plays a critical role in the organisation and synchronisation of swallowing (Jean, 2001). The NTS houses the primary sensory nucleus for the facial (CN VII), glossopharyngeal (CN IX) and vagus (CN X) nerves which relay information from the oral, pharyngeal and laryngeal regions to brainstem structures, respectively. Further, afferent connections from the trigeminal sensory nucleus in the pons have been detected in the NTS (Amri et al., 1984). Research has demonstrated that the NTS receives incoming cortical information that synapses on pontine relay nuclei, likely for modulation of the swallowing response during prandial ingestion (Miller, 2008). While stimulation of cortical areas has been found to elicit a swallowing response, lesioning of the dorsal medulla renders cortical areas unable to evoke a swallowing response following electrical stimulation, signalling its critical role in the amalgamation of afferent input (Miller, Bieger, & Concklin, 1997).

Once incoming sensory information is integrated, the NTS communicates with the ventral medullary centre. The NA contains the motor neurons responsible for relaying commands supplied by the NTS to the appropriate cranial nerves for activation (Miller, 2008). Thus, the activity of the NA is fundamentally dependent on the activation of the NTS to generate a patterned swallowing response (Amri et al., 1984). The NA contains the primary motor nuclei for the glossopharyngeal (CN IX), vagus (CN X) and spinal accessory nerves (XI), with associated efferent connections to the primary motor nuclei of the facial (CN VII), trigeminal (CN V) and the hypoglossal (CN XII) motor nucleus in the medulla. Critically, while the primary sensory nucleus for the vagus (CN X) nerve is in the NTS, vagal fibres, specifically the superior laryngeal nerve, directly connect with the NA to serve important airway protection mechanisms (Sugiyama et al., 2011). By directly communicating with the NA, a rapid response for a reflexive cough can be elicited through the ventral swallowing group, bypassing the NTS (Doty, Richmond, & Storey, 1967).

The cerebellum and the pons are not traditionally considered integral to the execution of the basic swallowing response, with predominant theories of deglutition focusing on control arising from the medulla (Lang, 2009; Miller, 2008). However, the pons, which is the most rostral section of the hindbrain, is intimately connected with the medulla, the cortex and the cerebellum, as well as home to numerous cranial nerves, such as the trigeminal nerve (CN V), abducens (CN VI) and facial (CN VII; Brodal & Bjaalie, 1992, 1997). CPGs for other

systems such as respiration and mastication are well represented in the pons (Abdala et al., 2009; Lund & Kolta, 2006, 2006; Molkov, Bacak, Dick, & Rybak, 2013; Morquette et al., 2012; Quintero et al., 2013; Rybak et al., 2004; St-John & Paton, 2004). Electrical stimulation in rabbits has revealed that regions in the pons and the pontine reticular formation are able to induce a swallowing response (Sumi, 1972).

Similar research highlights the possible role of the cerebellum in swallowing sensorimotor control (Rangarathnam, Kamarunas, & McCullough, 2014). The cerebellum is connected to the brainstem via three paired cerebellar peduncles and has a role in motor coordination and proprioception (Glickstein & Doron, 2008; Perrini, Tiezzi, Castagna, & Vannozzi, 2013). Efferent information from the cerebellum is primarily communicated through the superior cerebellar peduncle to the red nucleus and the thalamus, which is subsequently relayed to the cerebral cortex. The middle cerebellar peduncle is an afferent projection of pontine cells to the cerebellar cortex. Lastly, the inferior cerebellar peduncle consists of crossed efferent and afferent fibres arising from the posterior medulla (Glickstein & Doron, 2008). In early work, Mussen (1927) was able to elicit a swallow response following stimulation of the cerebellum, specifically the ventral vermis, in a cat model. Cerebellar elicitation of swallowing has been replicated in further studies (Berntson et al., 1973; Hockman, Bieger, & Weerasuriya, 1979; Martner, 1975). More recently, cerebellar activation has been evidenced with imaging of swallowing in healthy participants (Malandraki, Johnson, & Robbins, 2011; Malandraki, Sutton, Perlman, Karampinos, & Conway, 2009; Mosier & Bereznaya, 2001). However, in a meta-analysis of neuroanatomical predictors of dysphagia following stroke, Flowers et al. (2010) found no incidence of dysphagia following cerebellar infarct from a total of 656 subjects (Flowers, Skoretz, Streiner, Silver, & Martino, 2011). While it is highly likely the cerebellum plays a role in control or feed-forward/feed-back monitoring of swallowing due to its connectivity and anatomic proximity to critical swallowing-related centres, further research is needed to clearly specify the role and importance of these associated structures (Rangarathnam et al., 2014)

2.3 Cortical control of swallowing

Recent research using techniques such as functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), functional near infrared spectroscopy (fNIRS) and positron emission topography have contributed evidence that a complex array of cortical structures are

activated during swallowing (Barritt & Smithard, 2009; Hamdy, Rothwell, Aziz, & Thompson, 2000; Huckabee et al, 2003; Malandraki et al., 2011; Martin et al., 2004; Martin, Goodyear, Gati, & Menon, 2001; Mosier et al., 1999; Suntrup et al., 2013; Vasant et al., 2014). Such structures include the precentral gyrus, postcentral gyrus, premotor area, supplemental motor area, anterior cingulate cortex, operculum, insula, precuneus, cuneus, prefrontal area, temporal cortex, frontal cortex, internal capsule, association areas, thalamus and basal ganglia (Rangarathnam, Kamarunas, & McCullough, 2014). It is evident that, based on neuroimaging, the number of cortical centres involved in swallowing is substantial but somewhat non-specific. As explained by Leopold & Daniels (2010), "it might be concluded that nearly all cortical and subcortical gray region structures are activated during one of several pre-pharyngeal phases of ingestion. Depending on the context of each investigation, that conclusion may in fact be correct" (p. 255). With this broad level of activation, it becomes critical to analyse the specific methodology in each study and understand limitations of the various imaging techniques, such as fMRI requiring participants to maintain supine positioning. Studies of activation might better reflect cortical regions responsible for associated functions like tongue or jaw movements and planning, rather than reflecting swallowing related brain centres exclusively (Malandraki, Sutton, Perlman, Karampinos, & Conway, 2009). Further, imaging studies using blood-oxygen level dependent measures, such as fMRI or fNIRS, can measure activation but cannot differentiate between activation that is excitatory versus that which is inhibitory (Leopold & Daniels, 2010).

Historically, it has been accepted that only select parameters of swallowing are amenable to volitional alteration. For example, cortical regions were thought to trigger initiation of swallowing and control the oral phase of swallowing. Pharyngeal and oesophageal stages of swallowing, however, were believed to be carried out without any subsequent cortical input (Ertekin, 2011). Over time, however, further understanding of modulatory influence on the central pattern generator (CPG) driven pharyngeal swallow has suggested a greater capacity for cortical control of swallowing (Babaei et al., 2013; Hamdy et al., 1999, 2001; Huckabee et al., 2003; Martin, Goodyear, Gati, & Menon, 2001). As concluded by Humbert & German (2013), "there are tantalizing data that suggest various facets of oropharyngeal motor control and the interactions at various levels of the CNS during the normal swallow. However, the debate of whether the pharyngeal portion of the swallow is a reflex continues" (p. 8).

What is known, however, is that the cortex is critical in integrating sensory information prior to the initiation of a swallowing response. This allows appropriate adaptation of behaviour to meet incoming ingestive needs. The pre-oral phase relies initially on sensory input from sight and smell of a bolus. Relying on afferent processing from the optic (CN I) and olfactory (CN II) cranial nerves in the primary visual and olfactory cortices, respectively, bolus information can then be processed by association areas in the cortex for early initiation of preparation for swallowing (Martin et al., 2014). Following this, tactile and intra-oral afferent information, such as taste and temperature, can be integrated in regions such as the parietal cortex, posterior cingulate cortex, precuneus and somatosensory cortex, serving an association role in integrating sensory information (Hamdy et al., 1999; Miller, 2008; Steele & Miller, 2010). Research has indicated that the sensory strip is somatotopically mapped to represent regions corresponding the upper aerodigestive tract, including the face, tongue and pharyngeal regions (Mosier et al., 1999; Rangarathnam et al., 2014; Vasant et al., 2014). The provision of temporary oral anaesthesia has been associated with a reduction in somatosensory and motor area activation with MEG (Michou & Hamdy, 2009; Teismann et al., 2007). This cortical synthesis of sensory information has implications for patients after cortical stroke, for example, who may exhibit impairment in appropriately modulating a swallowing response to accommodate for various bolus types (Michou & Hamdy, 2009).

There is ongoing debate whether cortical control of swallowing is lateralised across hemispheres. Early evidence is provided by patients following stroke (Daniels & Foundas, 1999; Hamdy et al., 1997; Robbins, Levine, Maser, Rosenbek, & Kempster, 1993). Hamdy et al. (2004) evaluated electromyographic (EMG) responses after transcranial magnetic stimulation (TMS) of both the affected and unaffected hemispheres in 20 unilateral stroke patients (8 presenting with dysphagia). Dysphagic patients demonstrated reduced duration of pharyngeal EMG response than non-dysphagic patients, regardless of the lesion location (Hamdy et al., 1997). Robbins et al. (1993) evaluated patients with middle cerebral artery ischemic stroke (n = 40) compared to non-stroke controls (n = 20). Left-hemisphere lesions were associated with prolonged oral and pharyngeal transit durations, while right hemisphere lesions were associated with increased risk of aspiration and impaired initiation of pharyngeal swallowing. The authors suggested that their findings relate to cortical asymmetry in the control of swallowing. This has been expanded in recent theories, suggesting cortical control of swallowing to be bilateral, but asymmetric, with a ‘dominant’ hemisphere for swallowing

(Hamdy et al., 1997, 1999). This theory could aid in understanding variability in dysphagic presentations following unilateral impairment and in further understanding cortical reorganisation following stroke (Hamdy et al., 1997, 1999; Hamdy, Aziz, Thompson, & Rothwell, 2001). However, similar research suggests that components of swallowing may be controlled preferentially by either hemisphere or lateralization may be task-dependent (Daniels, Corey, Fraychinaud, DePolo & Foundas, 2006; Lowell, Reynolds, Chen, Horwitz & Ludlow, 2012).

In addition to the debate regarding lateralization, neural plasticity and potential maladaptive cortical plasticity are receiving increased attention (Humbert & German, 2013; Kleim & Jones, 2008; Malandraki et al., 2011; Martin, 2009; Robbins, Butler, Daniels, & Gross, 2008; Takeuchi & Izumi, 2012). Neural plasticity refers to the adaptive capacity of the CNS. Kleim and Jones (2008; p. S225) state "there is overwhelming evidence to indicate that the brain continuously remodels its neural circuitry in order to encode new experiences and enable behavioral change". This is critical when considering cortical response to neural impairment and subsequent rehabilitation. The foundational literature regarding neural plasticity arises from animal and limb studies. For example, it has been demonstrated in patients following unilateral stroke that rehabilitation constraining the unimpaired, ipsilesional upper limb improves not only the function of the impaired limb but stimulates activation in the remaining cortex of the injured hemisphere (Kleim & Jones, 2008). However, there are marked differences between swallowing neural control and control for corticospinal limb systems. Swallowing relies on a vastly different musculoskeletal framework, with midline muscle pairs that produce a large number of volitional and autonomic functions and a high-level of complexity in certain muscle groups (Martin, 2009). This is further complicated by uncertainty regarding lateralisation of cortical representation for swallowing, as discussed above (Martin, 2009).

Nevertheless, there is growing evidence that swallowing-related cortical centres can experience neural plasticity as a result of injury and plasticity associated with behavioural rehabilitation, similar to the limb literature (Martin, 2009). In a study of 28 patients with unilateral hemispheric stroke, evaluated longitudinally with TMS, an increase in pharyngeal representation was documented in recovered patients by the third month post-stroke onset. However, pharyngeal motor representations for non-dysphagic and non-recovered dysphagic

patients did not change in the unaffected hemisphere (Hamdy et al., 1998). These results indicate the possibility for cortical reorganisation of the swallowing system after injury. This holds promise for behavioural rehabilitation, with a new frontier of non-invasive stimulation techniques such as repetitive TMS and transcranial direct current stimulation receiving great attention in the literature (Doeltgen & Huckabee, 2012; Macrae, Jones, & Huckabee, 2014). Fundamental in the discussion of neural reorganisation is mention of the potential for maladaptive plasticity. Contrary to the positive effects of plasticity, cortical reorganisation has also been found to reduce motor recovery after stroke, especially in patients implementing compensatory strategies or experiencing a period of non-use, such as patients deemed unable to eat safely by mouth (Takeuchi & Izumi, 2012). While research regarding the ability of cortical structures to control, modulate and potentially negatively affect swallowing is ongoing and rapidly evolving, it is clear the cortex should not be underestimated in swallowing sensorimotor control.

Chapter 3: Biomechanics of Swallowing

Swallowing can be conceptualized as a pressure-driven event that enables coordinated transfer of a bolus through the upper aerodigestive tract (Perlman & Christensen, 1997). Swallowing is performed synergistically, both between areas, such as the oral, pharyngeal and oesophageal regions and across systems, such as respiration and mastication. To facilitate this synergy, swallowing biomechanics are dependent on strong integration of afferent sensory information. As stated by Steele & Miller (2010), "sensory input synaptically influences multiple pathways, both cortical and brainstem, to trigger swallowing, alter motor output and simultaneously activate ascending pathways, which reflexively modulate the motor output throughout the swallowing sequence" (p. 323).

In this chapter, biomechanics are discussed using conventional segmentation of the swallowing response into pre-oral, oral, pharyngeal and oesophageal phases (Huckabee & Daniels, 2008). While this framework is useful in conceptually segmenting the rapid and dynamic swallowing response into discrete elements, it should be noted that the onset and offset of each phase overlap (Martin-Harris, Michel, & Castell, 2005). Martin-Harris et al. (2005) highlighted these inconsistencies by measuring the temporal onsets of swallowing events to investigate the independence of the offset of the oral phase from the onset of the pharyngeal phase. Results indicated a marked overlap between structural and bolus flow measures from the oral and pharyngeal phases, illustrating "the artificiality of separating the swallowing continuum into isolated phases" (p. 283). Therefore, the following sections serve as a conceptual framework to discuss components of this tightly integrated, rapid response. It is important to remember the sensorimotor responses in each phase are dependent on and can affect, preceding and subsequent phases in this synergistic system.

3.1 Pre-oral phase

The pre-oral phase has been found to differ not only between animals and humans (Palmer, Rudin, Lara, & Crompton, 1992; Thexton, 1992), but between infants and adults (Lang, 2009; Selley, Ellis, Flack, & Brooks, 1990). The presentation of food or liquid stimulates the visual and auditory senses to begin the activation of neural structures responsible for the initiation of swallowing (Steele & Miller, 2010). Thus, the pre-oral phase contributes early information in the subsequent formation of an appropriate swallowing response, critical for

optimal swallowing function. This phase of swallowing is often underappreciated in clinical settings, for example, when patients dependent on others for feeding have reduced input from the sight, smell and tactile manipulation of food inherent in self-feeding (Kayser-Jones & Schell, 1997).

Pre-oral parameters of swallowing have an important role in priming the system for swallowing and ingestion. Relying on afferent processing from the optic (CN I) and olfactory (CN II) cranial nerves, sight and smell information can be processed by cortical areas for early preparation of swallowing (Steele & Miller, 2010). As discussed in Chapter 2, many cortical areas are responsible for processing this pre-oral information, such as the insular cortex, which integrates smell with taste input (Humbert & Joel, 2012). Further, inhalation of black pepper oil has been found to increase the number of swallows (Ebihara et al., 2006) and increase oral intake (Munakata et al., 2008), with an associated increase in regional cerebral blood flow in the insular and frontal cortices (Ebihara et al., 2006). With this afferent input, early physiologic responses are elicited in preparation for oral ingestion (Steele & Miller, 2010). Salivary flow is initiated from the submandibular and sublingual glands, innervated by the facial nerve (CN VII) and the parotid gland, innervated by the glossopharyngeal nerve (CN IX; Schneyer, Pigman, Hanahan, & Gilmore, 1956). Additionally, vocal adduction is initiated with activation of both interarytenoid and lateral cricoarytenoid muscles (Sasaki, Yu, Xu, Hundal, & Rosenblatt, 2006), innervated by the vagus nerve (CN X), as discussed in subsequent sections.

3.2 Oral Phase

The oral phase is largely considered to be under volitional control, despite mastication being controlled by a masticatory CPG (Morquette et al., 2012). This inconsistency is due to the ability to suspend or stop mastication voluntarily, which contrasts to the pharyngeal phase, which is considered an all-or-nothing response once initiated (Miller, 2002). The oral phase initiates with inhibition of the orbicularis oris by the facial nerve (CN VII; Ertekin et al., 2013), accommodated by relaxation of the primary muscles of mastication (e.g., masseter, temporalis) and activation of the muscles responsible for jaw opening (e.g., external pterygoid, submental muscle group). As the bolus enters the oral cavity, the lingual surface changes in shape through activation of the intrinsic lingual muscles to accommodate the

bolus in a midline groove (Miller, Sonies & Macedonia, 2003). The orbicularis oris actively contracts and the jaw closers are re-activated to return the mouth to closed position.

Once the bolus is inside the oral cavity, two phases commence, namely 'Stage I transport' responsible for transition of a solid food for mastication and 'Stage II transport' responsible for transition of the prepared bolus for deglutition (Palmer et al., 1992). Stage I transport consists of posterior movement of the pre-masticated bolus on the superior surface of the tongue, while the base of tongue approximates the palate to contain the bolus within the oral cavity (Taniguchi et al., 2013). This glossopalatal approximation is accomplished by activation of the palatoglossus, styloglossus, posterior belly of the digastric and stylohyoid, highlighting the redundancy in the swallowing system (Huckabee & Daniels, 2008). During Stage I, tongue rotation positions the pre-formed bolus on appropriate dental surfaces for mastication (Mikushi, Seki, Brodsky, Matsuo, & Palmer, 2014). The bolus mixes with saliva for breakdown and increased lubrication (Matsuo & Palmer, 2015; Taniguchi et al., 2013). This is accomplished with persistent sensory feedback from oral sensory receptors (CN VI, VII, IX) relaying afferent information about position and texture of the bolus and aiding in the guidance of tongue position (Steele & Miller, 2010). Taste is perceived with sensory receptors that primarily synapse at the level of the NTS, with supplementary taste information processed in cortical regions, including the insula and primary sensory cortex (Hamdy et al., 1999; Steele & Miller, 2010). Following Stage I transport, Stage II transport consists of upward movement of the tongue, transferring the bolus into the oropharynx with a wave-like movement (Matsuo & Palmer, 2015). The tongue tip and blade approximate the hard palate, pressing the bolus posteriorly out of the oral cavity. This serves to increase intra-oral pressure with systematic progression of pressure across the tongue surface (Matsuo & Palmer, 2015). Interestingly, Ali et al. (1997) placed a splint in the mouth of healthy adults (n = 15), creating a temporary tongue deformity (Ali, Cook, Laundl, Wallace, & de Carle, 1997). Results indicate that the presence of an altered lingual position and contour affected pharyngeal swallowing, with reduced peak pharyngeal pressure, reduced intrabolus pressure and delayed hyolaryngeal excursion (Ali et al., 1997). This highlights the importance of lingual propulsive action to the initiation of the pharyngeal phase.

3.3 Pharyngeal Phase

The initiation of the pharyngeal phase of swallowing is reliant on sufficient activation of oropharyngeal sensory receptor arrays, or 'sheets of sensory fibres' to stimulate the NTS, directly or indirectly through higher cortical pathways (Capra, 1995). The sensory regions involved in initiation of pharyngeal swallowing include the soft palate, uvula, tongue surface, faucial pillars, pharyngeal wall, pharyngeal surface of the epiglottis and vallecula (Miller and Sherrington, 1916; Pommerenke, 1928; Storey, 1968; Sinclair, 1970, 1971). Sensory stimuli that trigger and modulate swallowing have been found to respond tactile, nociceptive and thermal stimuli (Capra, 1995; Miller, 1972; Steele & Miller, 2010). As the oropharynx houses shared sensorimotor areas responsible for peripheral detection and production of protective responses such as gag, swallowing and emesis, accurate afferent sensory input is critical for the initiation of varied and appropriate responses (Capra, 1995; Miller, 1972). Mechanoreceptors widely distributed across the oral cavity and tongue can detect velocity of tissue displacement. This mechanical sensation from the posterior oral region, at the junction of the oral and nasal division, can elicit pharyngeal swallowing when paired with input from chemo- and thermosensitive receptors (Miller, 1972, 2002; Steele & Miller, 2010). Stephen et al. (2006) evaluated the position of the bolus head at initiation of the pharyngeal stage on VFSS in healthy volunteers (n = 10). The bolus head position at the onset of the swallow was typically below the level of the ramus of the mandible, with substantial variability across swallows (Stephen, Taves, Smith, & Martin, 2006). Sensory input can further modulate the contraction of muscles involved in the pharyngeal swallowing, with research indicating the duration of EMG activity increases as bolus volume and thickness increase (Hrychshyn & Basmajian, 1972).

Following successful activation of swallowing, the pharyngeal phase consists of a patterned response with numerous biomechanical movements, reflecting inhibition and activation of paired muscles in rapid succession. First, the tongue approximates the pharyngeal walls in a piston-like fashion to drive the bolus inferiorly, obliterating hypopharyngeal air space, as depicted in Figure 3.1 (Leonard, Kendall, Mckenzie, Ines Goncalves, & Walker, 2000). Base of tongue to posterior pharyngeal wall approximation occurs with activation of numerous muscles, such as the stylohyoid, posterior belly of the digastric, stylohyoid, styloglossus and glossopharyngeus (Jean, 2001). The mandible is then stabilized to enable hyoid bone movement (Miller, 2008). Superior and anterior hyoid movement is enabled through

contraction of the submental muscle group, namely the mylohyoid, geniohyoid and anterior belly of the digastric, with associated contraction of muscles aiding in superior hyoid movement, such as stylohyoid and the posterior belly of the digastric (Huckabee & Daniels, 2008). Recent research using fine-wire EMG in healthy participants (n = 14) has revealed that the geniohyoid has highest peak-adjusted EMG amplitude compared to the other submental musculature. Maximum EMG amplitudes for the anterior belly of the digastric varied according to bolus texture (Inokuchi et al., 2014). As postulated by the authors, this likely reflects modulation based on sensory responses originating in the oral cavity (Inokuchi et al., 2014). For example, it could be postulated that the geniohyoid has primary activation across textures, but the increased activation in the anterior belly of the digastric may play a role in greater anterior displacement of the hyoid bone with firm textures (Inokuchi et al., 2014).

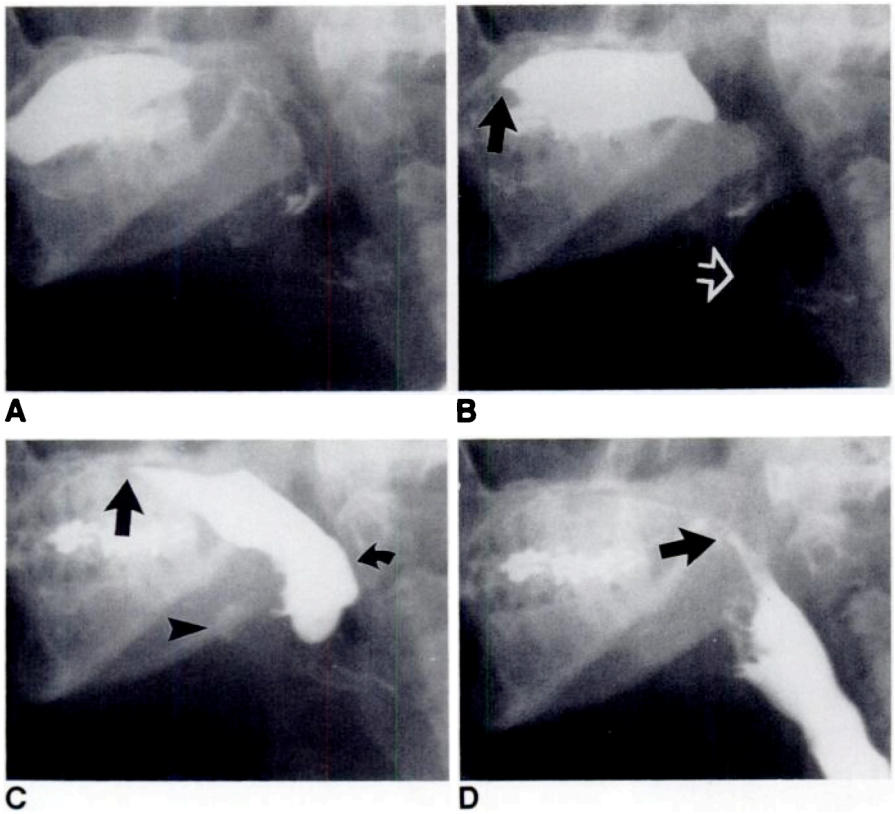


Figure 3.1 Initiation of the pharyngeal swallow from Dodds et al. (1990).[2] Image A reflects bolus position during the oral phase, with glossopalatal approximation sealing the posterior oral cavity. In frame B, the anterior tongue begins to contact the palate in preparation for

[2] Reprinted with permissions, Dodds, W. J., Stewart, E. T., & Logeman, J. a. (1990). Physiology pharyngeal and radiology of the normal phases of swallowing. American Journal of Roentgenology, 154, 953–963.

bolus transfer. Image C depicts continuation of tongue propulsive movement, with a drop in the tongue base providing deep sensory stimulation to contribute to the initiation of pharyngeal swallowing. Lastly, frame D shows maximal tongue base and posterior pharyngeal wall approximation, aiding in stripping the bolus through to the UES.

Anterior and superior hyolaryngeal excursion contribute to supraglottic shortening, epiglottic deflection and facilitate mechanical opening of the UES. The superior, middle and inferior pharyngeal constrictors are oriented obliquely (Miller, 2002). This allows not only a reduction of intraluminal space, but enables superior and posterior movement to maximize pharyngeal shortening (Miller, 2002). Figure 3.2 depicts the timing of activation of critical swallowing-related muscles (Jean, 2001). Notably, the majority of muscles fire nearly simultaneously, which contrasts to the peristaltic wave-like motion of the oesophagus, depicted on the right.

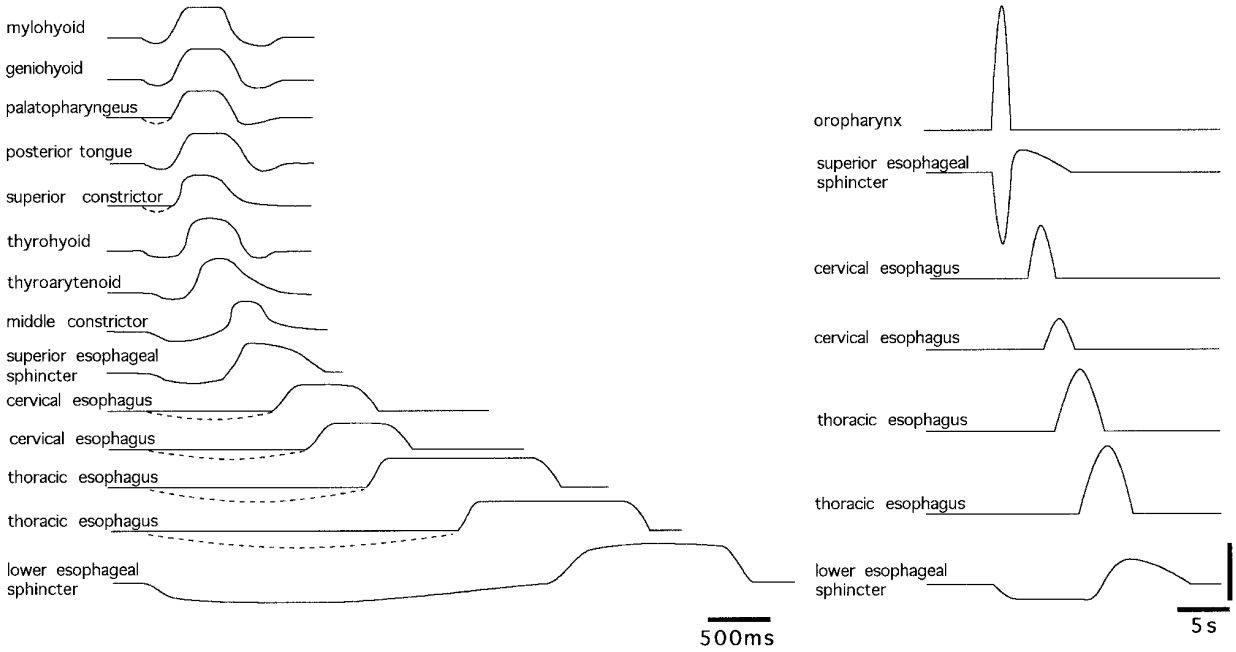


Figure 3.2 EMG waveforms summarizing patterned pharyngeal and oesophageal swallowing responses (Jean et al., 2001).[3]

The UES is comprised of the cricopharyngeus muscle, tonically contracted at rest, the thyropharyngeal portion of the inferior pharyngeal constrictor and rostral oesophageal

[3] Reprinted with permission of The American Physiological Society.

musculature (Williams, Pal, Brasseur, & Cook, 2001). The UES is relaxed through inhibition of the superior laryngeal nerve (CN X) innervating the cricopharyngeus muscle and opened by traction forces from anterior-superior hyolaryngeal movement. In a recent study by Jones et al. (2014), six healthy adults underwent simultaneous intramuscular EMG of the cricopharyngeus muscle and pharyngeal HRM of the UES. As expected, there was a positive correlation (r = 0.77 +/- 0.10) between UES EMG relaxation and nadir manometric UES pressures.

3.3.1 Airway Protection

The pharyngeal phase of swallowing is accompanied by numerous protective airway mechanisms, critical for maintaining safety during ingestion. As discussed in Chapter 2, sensation to the pharynx and larynx is provided by the vagus nerve (CN X), which provides sensory and motor information to elicit a cough response in the case of aspiration (Widdicombe & Fontana, 2006). Airway protection mechanisms can be separated into responses that aid in glottic closure or expel penetrated or aspirated bolus material (Widdicombe, Addington, Fontana, & Stephens, 2011). With regard to posterior glottic closure, the true and false vocal folds adduct through activation of the interarytenoid and lateral cricoarytenoid muscles (CN X). This contributes to a forward and downward tilting of the arytenoids to further close the glottic space (Dodds, Stewart, & Logeman, 1990). Further, as a result of epiglottic deflection, the quadrangular membrane becomes compressed over the anterior glottis, providing yet another layer of protection. Lastly, there is a brief apnoeic period during the pharyngeal phase, consisting of cessation of breathing during swallowing (Davenport, Bolser, & Morris, 2011; Kelly, Huckabee, Jones, & Carroll, 2007). Based on 320-row area detector computed tomography (CT) imaging, Inamoto et al. (2011) evaluated specific timing of laryngeal closure during swallowing. In healthy swallowing of liquids, it was revealed that closure of the true vocal folds, laryngeal vestibule and epiglottic inversion occurred almost simultaneously and was immediately followed by UES opening (Fujii et al., 2011; Inamoto et al., 2011).

Post-swallowing expiration and a continuum of cough responses serve as the primary airway protection mechanisms to actively expel bolus material (Widdicombe et al., 2011). In a study of swallowing-respiratory coordination of 20 healthy participants, Kelly et al. (2007) found the largest proportion of swallows occurred mid-expiration, with immediate post-swallow

expiration in voluntary, spontaneous and reflexive swallowing conditions (Kelly et al., 2007). This pattern allows post-swallow expiration to clear any trace penetration, supplemented by further layers of airway protection (Widdicombe et al., 2011). The two primary protective responses are the laryngeal expiration reflex and the cough reflex. Serving different functions, the laryngeal expiration reflex is not preceded by inhalation and consists of expiration with the goal of preventing material from passing below the level of the larynx. The cough reflex, contrastingly, commences with an inspiration and serves the purpose of clearing aspirant from within the tracheobronchial tree (Widdicombe & Fontana, 2006). Of note, the commencement of a cough response, whether voluntary or reflexive, begins with an inspiration, providing the opportunity for increased aspiration of bolus material should the resultant motor response be insufficient. As mentioned in Chapter 2, adequate sensation is critical with regard to production of an adequate and protective cough response, without which patients are at great risk for negative outcomes such as aspiration pneumonia (Miles et al., 2013).

3.4 Oesophageal Phase

In humans, the oesophagus is composed of striated muscles superiorly, with smooth muscles in the thoracic region (Goyal & Chaudhury, 2008). In contrast to the rapid pharyngeal phase, the oesophageal phase of swallowing can last over 10 s in a healthy subject (Jean, 2001). The oesophageal phase consists of a peristaltic wave propagating the bolus along the lumen and is completed when the bolus is propelled through the lower oesophageal sphincter (LES; Goyal & Chaudhury, 2008). Interestingly, the oesophagus has little to no EMG activity at rest, which may reflect deglutitive inhibition prior to peristaltic contraction (Jean, 2001). In repetitive swallowing, the oesophagus does not initiate a peristaltic wave until the last swallow, with a relaxed LES throughout. In contrast, the oesophagus can initiate a secondary peristaltic wave in the absence of a pharyngeal swallow in response to stimulation of oesophageal sensory receptors, aiding in clearance of residual bolus material (Goyal & Chaudhury, 2008).

Just as the oral stage of swallowing can affect timing and amplitude of pharyngeal biomechanics, as demonstrated in the Ali et al. (1997) study, oesophageal swallowing can affect the pharyngeal response and vice versa (Allen, White, Leonard, & Belafsky, 2012). In patients with a distal oesophageal impairment (e.g., ring), 58% of patients localized

symptoms to the neck region (Smith, Ott, Gelfand, & Chen, 1998). Similarly, Scharitzer et al. (2002) reported that of more than 3000 patients undergoing VFSS for evaluation of pharyngeal dysphagia, 14% (n = 434) presented with primarily oesophageal impairment, despite complaints of pharyngeal dysphagia and globus (Scharitzer et al., 2002). As stated by Allen et al. (2012), "up to one third of patients with the sensation of cervical dysphagia will have an esophageal cause for the symptom" (p. 264). O'Rourke et al. (2014) evaluated the effect of voluntary pharyngeal swallowing manoeuvres, including the Mendelsohn manoeuvre and effortful swallowing, on oesophageal physiology in healthy volunteers (n = 10). The voluntary manoeuvres affected the occurrence of non-peristaltic oesophageal swallowing responses, with fewer non-peristaltic swallows during effortful swallowing (33%) as compared to an increase during Mendelsohn manoeuvres (63%; O'Rourke et al., 2014). The ability of the pharyngeal phase of swallowing to directly affect the oesophageal response, highlights synergies in the complex modulation of sensorimotor control for swallowing.

Chapter 4: Evaluation of Swallowing Function

4.1 Measurement Integrity

Characterisation of swallowing for both research and clinical practice relies heavily on the use of instrumentation. Numerous factors, including reliability, sensitivity, specificity, generalizability and responsiveness, are key in determining whether the device or test is functioning optimally. Without keen understanding of instrument performance and possibility for error, understanding of the nature of dysphagia cannot be garnered with confidence. The potential for instrumental error is exacerbated by the required need for subjective interpretation, injecting bias as an additional source of error. Of the parameters critical to measurement integrity, Kimberlin & Winterstein (2008) argued that the reliability and validity of a tool are of the utmost importance. Reliability can be defined as the stability of the measures, both internally as well as across and within raters. Validity can be thought of as the extent to which the results reflect the accuracy of the true purpose the test was meant to serve (Kimberlin & Winterstein, 2008).

Reliability has been used to examine the stability of measurement at different time points (test-retest reliability) as well as within and across different ratings (intra- and inter-rater reliability). Reliability is measured on a scale from 0.0 to 1.0, with coefficients closer to 1.0 indicating greater reliability (Kimberlin & Winterstein, 2008). The stability of a measure is critical, especially in the evaluation of dysphagia in patients with acute neurologic impairment, for example, who may change rapidly in their presentation. As many tools used in the assessment of swallowing function rely on ratings made by clinicians and health care professionals, intra- and inter-rater reliability are paramount in understanding measurement differences within and between providers. Inter-rater reliability can assess the equivalence of ratings across examiners. There are numerous methods to quantify and compare inter-rater reliability. For example, the kappa statistic refers to a group of indices, including Cohen's, Fleiss's and weighted kappa, as described in Table 4.1. While there is debate regarding interpretation of kappa values, research suggests values of < 0.40 reflect poor to fair reliability, 0.41–0.75 reflect fair to good reliability and 0.61–0.80 reflect substantial reliability (Gisev, Bell, & Chen, 2013). Kappa values > 0.81 can be considered high reliability (Landis & Koch, 1977).

Table 4.1 Examples of inter-rater reliability indexes across varied levels of measurement; adapted from Gisev et al. (2013).

	Nominal / Categorical	**Ordinal**	**Interval / Ratio**
2 raters	Cohen's kappa; ICC	Weighted kappa; ICC	Bland-Altman plots; ICC
> 2 raters	Fleiss' kappa; ICC	Kendall coefficient of concordance; ICC	ICC

An alternate method of computing reliability is the intraclass correlation coefficient (ICC) (McGraw & Wong, 1996). This method is based on analysis of variance (ANOVA) models, originally applied to investigation of interval and ratio levels of measurement (Gisev et al., 2013). As seen in Table 4.1, ICC is a useful method for evaluating inter-rater reliability due to its flexibility in accommodating various levels of measurement and various numbers of raters. Similar to kappa, there are no standard values for acceptable reliability using ICC as the nature of the tool determines the precision necessary to judge acceptable reliability (Bruton, Conway, & Holgate, 2000). Importantly, however, if a measure demonstrates high reliability, it does not ensure strong validity, discussed below. Therefore, caution is needed when considering interpretation and application of a measures utility from reliability measures alone.

Validity refers to the ability of a test or tool to measure what it claims to measure. Importantly, although an evaluation method may have high reliability, it does not imply a high level of validity (George, Batterham, & Sullivan, 2000). For example, clinicians may be trained in performance of a rating methodology with great concordance, but, the rating may be inappropriate or based on incorrect interpretation, questioning the validity of the approach. Thus, validity is critical to probe the accuracy of the intended use or measurement (Kimberlin & Winterstein, 2008). Validity can be investigated through several means, such as determining face validity, content validity, or criterion validity. However, face and content validity methods largely relate to exploring validity of standardized tests and rating scales, for example. However, in the evaluation of dysphagia, the validity of measurement arises largely from establishing criterion validity. This form of validation compares results of an assessment tool to results of gold-standard methods, correlation to comparable methods and/or to relevant health outcomes of interest. Establishing appropriate criterion validity is

difficult in dysphagia research, as there are only select instrumental methods that can quantitatively evaluate swallowing biomechanics and the gold-standard in swallowing is debated (Langmore, 2003). Thus, a combination of adjuvant methods may be the superior practice pattern to best evaluate dysphagia, because "perfect validity, in design or measurement, is virtually unobtainable in human research science" (George et al., 2000; p. 121).

4.2 Clinical Examination

Due to the complex nature of oropharyngeal biomechanics, accurate screening, evaluation and diagnosis of dysphagia is critical to prevent negative secondary sequelae such as aspiration pneumonia or death. While a review of dysphagia assessment methods is beyond the scope of this thesis, the literature is clear that a bedside evaluation of swallowing function must have sufficient and balanced specificity and sensitivity for broad application to patients with possible dysphagia (Kertscher et al., 2014). Early and accurate detection of dysphagia can facilitate more rapid implementation of rehabilitation, which has been shown to reduce morbidity, length of stay and costs associated with care (Daniels, Ballo, Mahoney, & Foundas, 2000; Daniels, Anderson, & Willson, 2012).

The standard clinical bedside evaluation consists of analysis of behavioural indicators of swallowing safety, integrated with a thorough case history. As routine clinical bedside evaluations are largely subjective, research has revealed limitations in its validity and cost effectiveness (Baylow, Goldfarb, Taveira, & Steinberg, 2009; Wilson & Howe, 2012). Further, fewer than 50% of the measures clinicians typically employ at bedside are rated with sufficient inter- and intra-rater reliability for use in clinical practice (McCullough et al., 2000). These limitations can have a profound effect on patients, who may be misdiagnosed at bedside. For example, in patients with dysphagia secondary to neurologic impairment, cough reflex can be impaired or even absent. Consequently, this population can be without vital means of airway protection. This can result in silent aspiration, namely food or fluid entering the lungs without any immediate or detectable signs or symptoms (e.g., cough) (Addington, Stephens, & Gilliland, 1999; Miles et al., 2013). Given a reduced or absent response to aspirate, it is not surprising that standard bedside evaluations that subjectively analyse patient's behaviour when eating and drinking do not detect silent aspiration (Splaingard, Hutchins, Sulton, & Chaudhuri, 1988), leaving high-risk patients unidentified with an

increased risk of developing aspiration-related pneumonia (Miles et al., 2013). Therefore, adjuncts to the clinical bedside evaluation are critical for evaluation of the safety, efficacy and integrity of the oropharyngeal swallow.

There are methods available for further evaluating swallowing function at bedside with increased objectivity. One such test, termed cough reflex testing, simply consists of inhalation of nebulised citric acid or similar tussive agent (Bickerman & Barach, 1954) In individuals with a healthy sensory system, the citric acid will irritate the sensory receptors lining the larynx and lower airways and trigger a robust chain of reflexive coughs. In patients with dysphagia, the cough reflex can be impaired or even absent (Miles et al., 2013). Further adjuvant evaluation techniques include pulse oximetry (Collins & Bakheit, 1997; Ramsey, Smithard, & Kalra, 2006; Wang, Chang, Chen, & Hsiao, 2005), cervical auscultation (Borr, Hielscher-Fastabend, & Lücking, 2007; Leslie et al., 2007; Leslie, Drinnan, Finn, Ford, & Wilson, 2004) and bolus-related measures such as the Timed Test of Swallowing (Hughes & Wiles, 1996) and the Test of Masticating and Swallowing Solids (Athukorala, Jones, Sella, & Huckabee, 2014). Although these measures serve discrete roles in quantifying finite elements of pharyngeal swallowing, techniques such as pulse oximetry and cervical auscultation have been found to have questionable reliability and validity (Stroud, Lawrie, & Wiles, 2002; Wang et al., 2005). Further, bolus-related measures, such as the Timed Test of Swallowing and the Test of Masticating and Swallowing Solids, do not allow visualization of bolus flow or swallowing biomechanics. Therefore, the clinician is reliant on more comprehensive instrumental techniques to characterize dysphagia, prognosticate and determine optimal rehabilitation strategies. Two categories of instrumental techniques are discussed, namely visualization and pressure analysis.

4.3 Visualization

Visualization of swallowing function is critical for a thorough understanding of biomechanics, airway protection, anatomy and mucosal integrity. There are numerous methods for dynamic imaging of swallowing, namely VFSS (Logemann, 1983), videoendoscopic evaluation of swallowing (VEES; Bax, McFarlane, Green, & Miles, 2014; Langmore, Schatz, & Olsen, 1988; Leder & Murray, 2008; Lim et al., 2001), ultrasonography (Macrae, Jones, Myall, Melzer, & Huckabee, 2013), magnetic resonance imaging (MRI; Kreeft et al., 2012) and dynamic CT (Fujii et al., 2011; Inamoto et al., 2011). These

techniques can be thought of as complementary, with individual strengths and limitations. For example, although dynamic CT imaging provides unparalleled three-dimensional analysis of swallowing, it is limited by expense and substantial radiation exposure, and is therefore limited to use in specialized research laboratories (Fujii et al., 2011; Inamoto et al., 2011; Kobayashi, Koshida, Suzuki, & Katada, 2012). Contrastingly, ultrasonography is non-invasive and widely available in health care settings, however, it only reliably provides a narrow insight into lingual surface movement, hyoid movement and two-dimensional muscle diameter (Macrae, Doeltgen, Jones, & Huckabee, 2012; Macrae et al., 2013).

The two most widely utilized visualization techniques are VFSS and VEES (Langmore, 2003). Both VFSS and VEES can be performed across the lifespan, in nearly all dysphagic aetiologies and has been proven to be superior than clinical bedside evaluations alone (Wilson & Howe, 2012). VEES which consists of trans-nasal insertion of a fibreoptic endoscope to record intra-luminal swallowing (Bax et al., 2014; Lim et al., 2001; Tohara et al., 2010). VEES examinations have superior capability for evaluation of mucosal and anatomic integrity given direct visualization of the soft-tissue structures. With no radiation exposure, VEES can be used as a training and biofeedback tool during rehabilitation without contraindications inherent in repeating procedure (Langmore et al., 1988). However, VEES has notable limitations, including a 'white-out' period during peak pharyngeal swallowing due to intraluminal constriction obscuring the recording from the endoscope. Further, VEES cannot provide information regarding oral and oesophageal phases of swallowing or evaluate critical biomechanics such as hyoid movement. Research indicates ratings of aspiration (Kelly, Drinnan, & Leslie, 2007) and residue (Kelly, Leslie, Beale, Payten, & Drinnan, 2006) are significantly higher following evaluation with VEES as compared to VFSS.

VFSS is largely considered the gold-standard in evaluation of deglutition as it can visualize all stages of swallowing as an integrated process (Rugiu, 2007) and has been utilized in research and clinical practice for over thirty years (Logemann, 1983). VFSS uses ionizing radiation to visualize a bolus impregnated with a contrast agent, typically barium. This instrumentation provides two-dimensional, dynamic, radiographic images of swallowing, allowing frame-by-frame analysis of ingestive biomechanics (Feinberg, 1993). VFSS evaluates temporal characteristics of swallowing, including duration and onset of swallowing phases (Fox et al., 2014; Leonard et al., 2000; Leonard, Rees, Belafsky, & Allen, 2011),

kinematic events (Bardan, Kern, Arndorfer, Hofmann, & Shaker, 2006; Humbert et al., 2013; Macrae, Anderson, Taylor-Kamara, & Humbert, 2014; Sia, Carvajal, Carnaby-Mann, & Crary, 2012), integrity of airway protection (Feinberg, 1993; Hind et al., 2009; Kelly et al., 2007; Robbins, Coyle, Rosenbek, Roecker, & Wood, 1999) and effects of compensation (Baylow et al., 2009; Bülow, Olsson, & Ekberg, 1999, 2001, 2002). Further, patient performance on VFSS has been linked with important predictive outcomes. In a study comparing patients with dysphagia (n = 26) to case matched controls (n = 33), Schmidt et al. (1994) found that of patients who aspirated thickened liquids or more solid consistencies on VFSS, the odds ratio for developing pneumonia was 5.6 times greater compared with those who did not aspirate, or who aspirated thin liquids only. Further, the odds ratio for death was 9.2 times greater for patients who aspirated thickened liquids and more solid consistencies compared with those who did not aspirate or who aspirated thin liquids only (Schmidt, Holas, Halvorson, & Reding, 1994).

Despite the undisputed utility of VFSS, there are limitations. It exposes patients to ionizing radiation, which can have short and long-term health implications. Dose is related to screening time and acquisition/frame rate, which is dependent on the complexity of the swallowing assessment and patient compliance (Wright et al., 1998). Nevertheless, doses recorded in reviews of exposure in clinical practice are < 1.23 mSv (SD = 0.64) (Kim et al., 2013), which compares favourably to a single full-body CT-scan of 10 to 30 mSv (Brenner & Hall, 2007). Results have indicated more than 40 VFSS examinations would need to be administered per year to exceed an individual's annual radiation dose exposure limit (Kim et al., 2013).

Additionally, researchers have highlighted pronounced concerns regarding reliability in interpretation of VFSS. Ekberg et al. (1998) investigated reliability of radiologists scoring VFSS. While the highest reliability was found for identification of aspiration (k = 0.83), the lowest concurrence was for critical swallowing parameters such as decreased or absent pharyngeal constriction and delayed opening of the UES (k < 0.40). Even in implementation of standard protocols, reliability has been found to be similarly poor (k = 0.01–0.56) (Stoeckli, Huisman, Seifert, & Martin-Harris, 2003). This poor agreement has been replicated with Speech-Language Pathologists in similar studies (Kuhlemeier, Yates, & Palmer, 1998; Scott, Perry, & Bench, 1998). In a recent systematic review, Baijens et al. (2013) reported

measurements in VFSS varied considerably with ICC between 0.22–0.84, depending on method of measurement, pre-experimental training and bolus consistency used. The authors report studies investigating intra- and interrater reliability VFSS measurements were of poor methodological quality (Baijens, Barikroo, & Pilz, 2013). Increases in inter-rater reliability to greater that 80% have been achieved with standard protocols (Martin-Harris et al., 2008) but these programmes require criterion-referenced training and the development of the rating protocol was not available for stringent peer review due to commercialisation concerns, raising concerns regarding validity. Further, VFSS cannot provide information on the underlying nature of impairment, such as weakness, spasticity, apraxia, or other neuromuscular change. Although impaired biomechanics may be observed, this observation cannot define the underlying pathophysiology. Although undoubtedly a valuable tool for visualising swallowing biomechanics, the widespread dependence on VFSS in isolation may be contributing to misdiagnosis in the evaluation of dysphagia. There is a need for more objective adjuncts to make the current gold standard diagnostic imaging technique less biased and increasingly robust.

4.4 Pressure Analysis

Pharyngeal manometry is the only method of quantifying pressure in the pharynx during swallowing. It has been used for more than twenty years to objectively evaluate numerous parameters of swallowing physiology (Castell & Castell, 1993; Dodds, Kahrilas, Dent, & Hogan, 1987). Despite this, pharyngeal manometry has been slow to emerge into routine clinical practice (Ravich, 1995). In a recent survey of 206 speech-language pathologists, Jones et al. (2014) documented only 3.5% of respondents reported having access to manometry in their workplace. This is compounded by the finding that of those who had access to manometry, only half reported they would pursue further manometric evaluation in a case study of a patient presenting with UES dysfunction (Jones, Knigge, & McCulloch, 2014). This highlights the need for continued education regarding the utility of this technique and increased inter-disciplinary access, as it is one of the few tools in the diagnostic armamentarium that can provide objective assessment with high temporal resolution.

4.4.1 Low-resolution Manometry

Low-resolution, solid-state manometry, developed primarily for use in the oesophagus, was an advancement on traditional water-perfusion techniques (Dodds et al., 1987). While the

exact specifications may vary, this technique provides quantitative analysis of swallowing at three discrete points: the proximal pharynx at approximately the base of tongue region, the distal pharynx at approximately the level of the laryngeal additus and the region of the UES (Salassa et al., 1998). The majority of research using low-resolution manometric catheters comply with published standards, namely utilization of a 100-cm-long ovoid catheter, 2.1 mm in diameter (Kahrilas & Shi, 1998; Salassa, DeVault, & McConnel, 1998). Under these recommendations, the catheter should house 3 solid-state, unidirectional, posteriorly-oriented sensors (2 x 5 mm), with 2 cm spacing between sensors 1 and 2, and 3 cm between sensors 2 and 3 (Salassa et al., 1998). A fourth, optional, sensor can be included for measurement of the proximal oesophagus.

As early as 1987, researchers were questioning the appropriateness of these recommendations, specifically the use of unidirectional measurement sensors in a non-uniform lumen, with highly variable lateral versus anterior and posterior closing forces (Dodds et al., 1987). Previous publications have reported that radial asymmetry in pressure measurement can vary as high as 86 ± 13 to 365 ± 29 in lateral and posterior directions, respectively (Castell & Castell, 1993). This is compounded by inability to confirm specific intraluminal catheter placement when performing manometry without adjunct visualization techniques. Doeltgen et al. (2007) evaluated the intraluminal placement of a 2.1-mm diameter catheter following insertion in either the right or left nares in healthy participants (n = 10). Based on analysis of still radiographic images, the catheter was positioned in the pharyngeal midline for only 20% of trials, with a deviation from 1.7 to 14.7 mm from midline (Doeltgen et al., 2007). However, the use of circumferential sensors is similarly flawed in this regard; additionally, in most cases circumferential sensors impose an increased catheter diameter which may contribute to increased patient discomfort and inability to generalise to existing normative pharyngeal pressure data from 2.1-mm diameter unidirectional catheters (Salassa et al., 1998).

Whether using unidirectional or circumferential sensors, low-resolution manometric catheters are typically positioned with a pull–through technique, performed in 5-mm increments (Castell & Castell, 1993). Once the catheter is inserted transnasally to a depth of 25 cm or greater from the nose, the catheter is slowly removed until placement can be confirmed through visualization of a characteristic ‘M’ wave displayed at Sensor 3 (Figure 4.1). The

'M' wave pressure profile is produced during swallowing as a result of the following sequence. First, when the sensor is placed at the superior aspect of the resting UES, a positive baseline pressure can be recorded. At the onset of swallowing, hyolaryngeal excursion will facilitate a rise in the position of the UES to lie directly over the sensor, increasing the baseline pressure. Then, a decrease in recorded pressure will follow, representing relaxation of the UES. At the offset of the pharyngeal swallow, a rise in pressure will again be recording, aligning with a return of active contraction of the UES. This is followed by a reduction in baseline pressure, achieved by hyolaryngeal descent enabling UES return to rest position. (Castell & Castell, 1993). Thus, the characteristic 'M' wave has been considered suitable for use in blind placement, indicating the lowermost sensor is located at the proximal border of the high pressure zone of the UES (Castell et al., 1995).

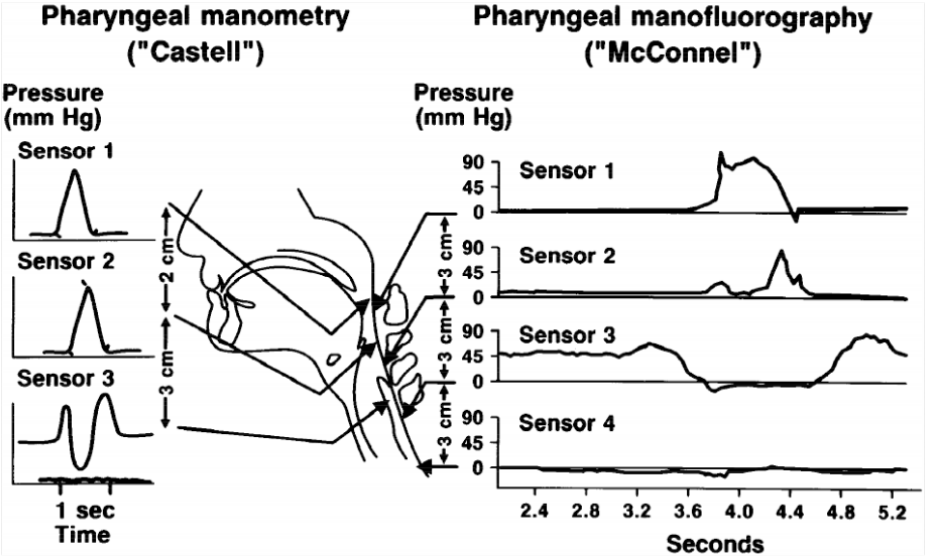


Figure 4.1 Schematic of typical pressure profiles using a 3 ("Castell") or 4 ("McConnel") sensor standardized manometric catheter (Salassa et al., 1998).[4] Note the characteristic 'M' wave pattern depicted in sensor 3 in both catheter types.

Although use of the 'M' wave for catheter positioning and placement is published routinely (Al-toubi, Doeltgen, Daniels, Corey, & Huckabee, 2015; Balou et al., 2014; Huckabee & Steele, 2006; Lamvik, Macrae, Doeltgen, Collings, & Huckabee, 2014; Witte, Huckabee, Doeltgen, Gumbley, & Robb, 2008), the validity and reliability of this catheter positioning

[4] Reprinted with permission of Springer Dysphagia, Proposed catheter standards for pharyngeal manofluorography (videomanometry), 13, 1998, 107, Salassa, J., DeVault, K.,McConnel, F.

technique warrants further investigation. Of note, original publications describing use of the M-wave did not validate against VFSS (Castell & Castell, 1993). This is critical, as inappropriate positioning based on the 'M' wave can, for example, misdiagnose a patient with impaired UES functioning. If a patient has sufficient hyolaryngeal excursion, it is possible that inappropriate placement can lead to the sensor measuring pressure from the cervical oesophagus, a negative pressure zone, artificially reducing the nadir pressure measured in the UES sensor. Further, differences in UES placement can affect duration measurements as well. Kahrilas et al. (1988) investigated four methods of investigating the duration of UES opening, including VFSS, manometric measurement of the highest pressure UES zone, manometric measurement of a superior UES high pressure zone and a sleeve sensor spanning the UES region. The timing of UES opening was similar with a range of 0.42–0.53 s for all techniques except measurement of UES pressure at a superior UES pressure zone, recommended in 'M' wave placement. This method recorded an increased relaxation duration of 0.74 s (Castell & Castell, 1993; Kahrilas, Dodds, Dent, Logemann, & Shaker, 1988). The poor understanding of the reliability and validity of the 'M' wave is highlighted in recent research with HRM, discussed in the subsequent section, where the UES has been found to readily span 4–6 pressure sensors (Jones, Ciucci, Hammer, & McCulloch, 2015).

Previous publications have explored the stability of measures across sessions and the correlation of manometric measurements with other instrumentation devices. Macrae et al. (2011) reported an investigation of within-subject variance and order effects in the manometric evaluation of healthy participants (n = 20) within and across three sessions. Results indicated a high correlation between the variance across and within sessions (r = 0.92), with no significant effects of trial or session for dry and liquid swallowing across sensors. Macrae et al. (2011) estimated the greatest change across trials was no larger than 5% and the maximum change across sessions was no larger than 12%. These findings are supported by two additional studies finding no significant effect of trial on measurement of pressure, onset or duration of pharyngeal pressure (Butler et al., 2009; Hiss & Huckabee, 2005).

These important results are supplemented by studies correlating the findings of manometry to other more established techniques to evaluate pharyngeal swallowing. For example, Pauloski

et al. (2009) evaluated the relationship between VFSS and manometry in healthy adults (n = 7) and dysphagic patients (n = 11). Results indicated a significant relationship between these two evaluation techniques, with correlation between increases in amplitude of pharyngeal pressure with duration of tongue base to posterior pharyngeal wall approximation. Further, duration of pharyngeal pressure was correlated with bolus transit times, with greater pharyngeal residue associated with increased pressure duration (Pauloski et al., 2009). These findings are mirrored in a more recent study by Leonard et al. (2011) who evaluated the relationship between pharyngeal manometry and a measure of pharyngeal constriction on VFSS in dysphagia patients (n = 25). A significant inverse correlation (r = -0.72) was identified between manometric pressure and pharyngeal constriction ratio, indicative of functional obliteration of the intraluminal pharyngeal airspace during swallowing. In a study by Lang et al. (1991), healthy canines underwent simultaneous videofluoroscopy, intramuscular EMG of the cricopharyngeus muscle and pharyngeal manometry of the UES. There was a positive correlation ($r = 0.87$; $p < .01$) between UES EMG relaxation and nadir UES manometric pressures (Lang, Dantas, Cook, & Dodds, 1991). Lastly, Huckabee et al. (2005) investigated the correlation between surface electromyography (sEMG) of the submental muscle group to manometric measures in effortful and noneffortful swallows performed by healthy adults (n = 22). Results indicated there was a significant but weak correlation between manometry and sEMG, considered to be a weak predictor of pharyngeal pressure.

Further research indicates pharyngeal manometry to be sensitive to differences in swallowing conditions, such as spontaneous versus reflexive swallowing and variable bolus sizes. Al-Toubi et al. (2015) investigated manometric pressure in healthy participants (n = 24) performing four swallowing conditions, including discrete saliva swallowing, discrete 10 mL water swallowing, volitional continuous water swallowing and reflexive continuous water swallowing, with water injected directly to the pharynx. Manometric measures varied significantly across swallowing tasks, indicating that this measure is able to record and discriminate differences in swallowing conditions. Discrete swallowing was found to contribute to lower nadir UES pressure more than continuous ingestion, similar to a lower nadir pressure in saliva swallowing than liquid swallowing (Al-toubi et al., 2015). Further, discrete swallowing produced longer pharyngeal pressure, UES opening and overall

swallowing durations than continuous swallowing, similar to results of prior research (Witte et al., 2008).

Normative data exists regarding the amplitude and duration of pharyngeal pressure, degree of UES relaxation and the coordination of timing of UES relaxation relative to pharyngeal pressures (Butler et al., 2009). Studies have revealed differences based on gender and age (Butler et al., 2009; Meier-Ewert et al., 2001; van Herwaarden et al., 2003). Lamvik et al., (2014) reported the largest normative dataset to date, with healthy participants (n = 80) stratified by age and gender. Normative values can be found in Tables 4.2 and 4.3 below (Lamvik et al., 2014). These data provide a reference for clinical assessment of patients presenting with swallowing impairment. For example, pharyngeal manometry has been used to document dysphagia in various populations of patients, including stroke (Martino et al., 2001; Bülow et al., 1999), Parkinson's disease (PD) (Sung et al., 2010; Ali et al., 1996), head and neck cancer (Lazarus et al., 2002) and other rare syndromes (Katsanos et al., 2001; Higo et al., 2005; Gomes et al., 2008). Additionally, modification of pressures resulting from various swallowing manoeuvres have been investigated using pharyngeal manometry, such as effortful swallowing, supraglottic swallowing, tongue-hold swallowing and the Mendelsohn manoeuvre (Bülow et al., 1999; Bülow et al., 2001; Doeltgen et al., 2009; Doeltgen et al., 2011; Fukuoka et al., 2013; Hoffman et al., 2012; Hind et al., 2001; Huckabee & Steele, 2006; Huckabee et al., 2005; Hiss & Huckabee, 2005; Lever et al., 2007; Takasaki et al., 2011). These studies investigate the characteristics of pharyngeal biomechanics associated with disorders and treatment and supplement normative data in the evaluation and rehabilitation of patients with dysphagia. This may aid in encouraging the application of pharyngeal manometry in routine clinical practice, given its utility in generating quantitative diagnostic information (Ravich, 1995).

Table 4.2 Average Temporal Durations (ms) of Pharyngeal Swallowing by Age and Gender.

Saliva Swallowing	Peak Sensor 1-2	UES Duration
Young Females	209 (95% CI 190-230)	1073 (95% CI 1010-1130)
Young Males	258 (95% CI 250-270)	1193 (95%CI 1130-1250)
Older Females	236 (95% CI 220-260)	1006 (95% CI 960-1060)
Older Males	254 (95% CI 220-280)	1047 (95% CI 990-1110)
Total Cohort	**239 (95% CI 215-263)**	**1080 (95% CI 1023-1137)**

Table 4.3 Average Amplitude (mmHg) of Pharyngeal Swallowing by Age and Gender.

Saliva Swallowing	Sensor 1 (95% CI)	Sensor 2 (95% CI)	Sensor 3 (95% CI)
Young Females	97.9 (84.9-110.8)	122.9 (103.7-142.3)	-10.5 (-13.2- -7.7)
Young Males	127.9 (103.7-152.0)	109.1 (96.8-121.4)	-9.6 (-12.4- -6.8)
Older Females	114.7 (88.2-141.2)	109.9 (87.7-131.9)	-9.2 (-11.4- -6.9)
Older Males	116.1 (94.9-137.1)	105.0 (79.5-130.6)	-7.3 (-9.4- -5.3)
Total Cohort	**113.9 (103.6-123.4)**	**111.8 (102.1-121.5)**	**-9.1 (-10.3- -7.9)**
10 mL Bolus Swallowing	Sensor 1 (95% CI)	Sensor 2 (95% CI)	Sensor 3 (95% CI)
Young Females	90.7 (83.7-97.6)	98.3 (91-3-105.3)	-4.1 (-5.1- -2.9)
Young Males	98.6 (90.8-106.5)	87.8 (83.2-92.3)	-8.5 (-9.6- -7.5)
Older Females	99.6 (86.5-112.7)	92.0 (84.2-99.8)	-5.1 (-6.3- -3.9)
Older Males	132.2 (116.9-147.5)	97.9 (88.6-107.3)	-3.9 (-4.9- -2.9)
Total Cohort	**105.4 (99.6-111.2)**	**94.1 (90.4-97.7)**	**-5.4 (-5.9- -4.9)**

While a typical VFSS is recorded at a maximum of 30 frames per second, low-resolution pharyngeal manometry can provide temporal information in the millisecond range (Barbiera et al., 2006). Therefore, low-resolution manometry can be paired with VFSS, termed manofluoroscopy, to directly visualize swallowing events time-locked with analysis of temporal and amplitude pharyngeal pressure parameters (Goeleven et al., 2006; McConnel et al., 1988; Feinberg, 1993; Kahrilas & Shi, 1998; Salassa et al., 1998; Rommel et al., 2006; Bodén et al., 2006). Manofluoroscopy is considered the gold standard in evaluation of swallowing function (Nativ-Zeltzer, Kahrilas, & Logemann, 2012).

The primary limitation of three-channel pharyngeal manometry is sensor positioning, arising from fixed sensor placement along the catheter, intra-swallow movement altering the location of the sensors within the lumen and questions regarding the appropriateness of the 'M' wave in guiding placement, as discussed above. Research indicates a typical pharynx can range between 7–13 cm in healthy individuals (Ergun, Kahrilas, & Logemann, 1993). With fixed sensor positions along the catheter, measurement accuracy may be reduced across individuals of varying height. Further, users of low-resolution pharyngeal manometry must be cautious of this intra-swallow catheter movement altering recording location of each sensor area, especially in blind manometric studies where catheter placement is not visually confirmed

with VFSS. Intra-swallow catheter movement is thought to arise from early movement resulting from velopharyngeal closure, followed by a non-synchronous change in the length of the pharynx and position of the UES (Ravich, 1995). One method to overcome this limitation is to calculate a pharyngeal composite score to represent average overall pharyngeal pressure generation from the base of tongue region to the distal pharyngeal area at the level of the laryngeal additus (Lamvik et al., 2014). Normative data have been reported for pharyngeal composite scores, comparable to the average of pressure generation for Sensor 1 and 2 for each swallowing condition, as reported in Table 4.4. This score can be used for comparison of overall pharyngeal pressure generation with basic manometric assessments. By decreasing the sensitivity of the values to changes in position due to movement artefact and comparison to just one number rather than comparison of individual sensors, this simple pharyngeal composite calculation has potential for clinical utility. However, this may reduce measurement specificity and this score does not aid correction of UES measurement, which remains highly sensitive to intra-catheter movement and initial catheter placement and may decrease specificity in measurement by averaging across the pharyngeal area.

Table 4.4 Pharyngeal Composite across Swallowing Types by Age and Gender (mmHg).

Pharyngeal Composite (95% CI)	*Saliva Swallowing*	*10 mL Bolus Swallowing*	*Effortful Swallowing*
Young Females	110.4 (98.6-122.2)	94.5 (89.6-99.4)	122.3 (107.4-137.1)
Young Males	118.5 (105.2-131.8)	93.2 (88.6-97.8)	121.5 (106.1-136.9)
Older Females	112.3 (95.8-128.7)	95.8 (88.2-103.3)	113.2 (99.1-127.3)
Older Males	110.5 (94.6-126.4)	115.6 (106.1-125.0)	132.5 (111.5-153.5)
Total Cohort	**112.9 (105.8-119.9)**	**99.7 (96.2-97.8)**	**122.4 (114.4-130.9)**

Low-resolution manometry is a highly useful adjunct to clinical evaluations, providing robust, quantitative data regarding pharyngeal and UES functioning with high temporal resolutions. Although HRM advances this technology, as discussed in the subsequent section, far fewer clinicians have access to this sophisticated equipment. Therefore, low-resolution manometry remains more readily available and therefore still clinically relevant to research and clinical practice.

4.4.2 High-resolution Manometry

The advent of high-resolution manometry has overcome many of the limitations of conventional, low-resolution pharyngeal manometry. By increasing the number of recording sensors from 3 or 4 to 36, HRM enables continuous evaluation of intraluminal pressure along the aerodigestive tract. Each of the 36 pressure sensors is comprised of up to 16 measurement segments, creating an averaged, circumferential pressure reading within each sensor. These intraluminal pressures can be displayed as waveforms, similar to low-resolution manometry, and as a topographical plot, displayed in Figure 4.2. In most HRM catheters, sensors are spaced at most 1 cm apart, with the capability to interpolate pressure between the recording sensors. This inherently improves the reliability of measurement, as the uppermost sensor can be positioned immediately inside the naris in all participants and the length of the upper aerodigestive tract can be evaluated in its entirety. With robust spatial resolution paired with high temporal resolution, pharyngeal HRM has become increasingly common in research (Hoffman et al., 2013; Hoffman, Ciucci, Mielens, Jiang, & McCulloch, 2010; Knigge, Thibeault, & McCulloch, 2014; Mielens, Hoffman, Ciucci, Mcculloch, & Jiang, 2012; Pandolfino, Fox, Bredenoord, & Kahrilas, 2009; Takasaki et al., 2008).

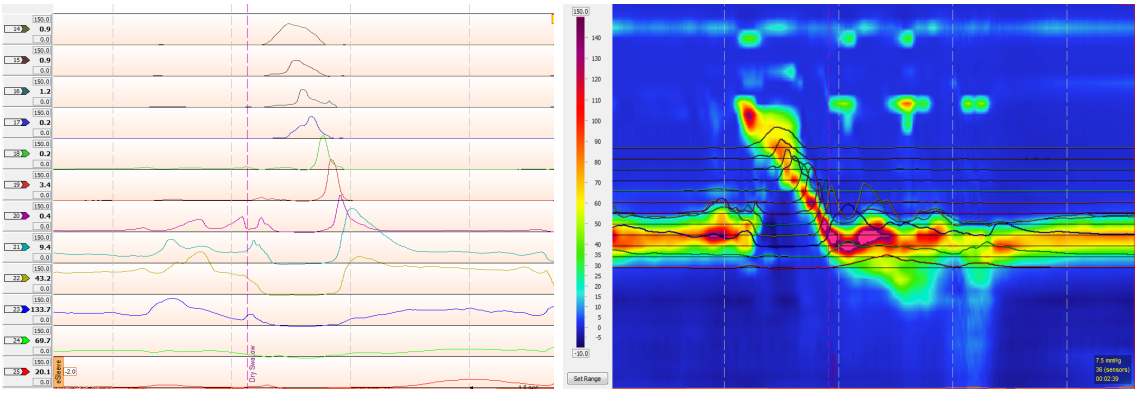


Figure 4. 2 Example swallow depicted on HRM. The image on the left is a waveform view, typical for users familiar with low-resolution manometry. On the right, the same swallow is visualized as a topographical plot. Sensors are represented along the y-axis, with time represented along the x-axis. Pressure is signified by colour, with warmer colours indicative of higher pressure.

Pharyngeal HRM has been used to evaluate normal swallowing (Takasaki et al., 2008) and swallowing using various manoeuvres, including tongue hold (Hammer, Jones, Mielens,

Kim, & McCulloch, 2009), effortful swallowing (Hoffman et al., 2012; Takasaki, Umeki, Hara, Kumagami, & Takahashi, 2011), Mendelsohn manoeuvre (Hoffman et al., 2012), head turn (Balou et al., 2014; McCulloch, 2010) and chin tuck (Balou et al., 2014; McCulloch, 2010). Differences in bolus sizes and textures have additionally been evaluated (Lin et al., 2014; Ryu, Park, Oh, Lee, & Kang, 2015). Further, pharyngeal HRM has been used to evaluate pharyngeal dysphagia in patients with stroke (Lan et al., 2015), PD (Suttrup & Warnecke, 2015), myotonic dystrophy (Jungheim, Kühn, & Ptok, 2015) and Huntington's disease (Tae Hee Lee, Lee, & Kim, 2012).

However, despite the increasing number of publications reporting this advanced instrumentation, there are notable limitations of pharyngeal HRM with regard to analyses and the potential for measurement error in recordings. Currently, there no commercially integrated platforms available for analysis of pharyngeal swallowing, with the exception of the UES (Lee et al., 2014). Although ongoing work is exploring classification models of pharyngeal swallowing similar to those used in oesophageal analysis (Mielens, Hoffman, Ciucci, Jiang, & McCulloch, 2011), there is no consensus on optimal measurements of pharyngeal HRM. In the first publication investigating pharyngeal HRM, Takasaki et al. (2008) performed a feasibility study to assess the potential for application of HRM in oropharyngeal swallowing. The investigators assessed healthy volunteers (n = 33) with a standard 4.2 mm pharyngeal HRM catheter. Normative data were recorded during ingestion of three dry swallows and three 5 mL water swallows. Higher amplitude with increased variability was documented when compared to normative data in low-resolution manometry (Lamvik et al., 2014). For example, in young males, low-resolution manometry revealed a pharyngeal composite amplitude (average of tongue base pressure and hypopharynx) of 118.5 mmHg (105.2–131.8; Lamvik et al. 2014) while in HRM, meso-hypopharyngeal amplitude (average of tongue base pressure and hypopharynx) was 175.3 mmHg (115.6–235; Takasaki et al., 2008). This difference could arise from using unidirectional versus circumferential sensors. However, inherent in this difference is catheter diameter, as circumferential sensors contribute to a larger catheter diameter than unidirectional sensors. The difference between low- and high-resolution manometric catheters is substantial – a 2.1 mm increase with a diameter of up to 4.2 mm in HRM systems. In a study evaluating within-subject differences in swallowing as a result of catheter diameter, Xiang et al. (2013) evaluated healthy (n=9) and dysphagic (n=18) participants with 4.2 mm and 2.7 mm diameter HRM catheters.

Although predominantly evaluating oesophageal functioning, the authors found higher resting UES pressures with the 4.2 mm catheter and called for development of diameter-specific normative data (Xiang et al., 2013). Further research is needed regarding differences in timing and amplitude of pharyngeal pressure with HRM catheters of varying diameter.

Nevertheless, while the work by Takasaki et al. (2008) provided feasibility data to support use of pharyngeal HRM, it also set standard measurement methodology. They advocated selection of three anatomic regions for measurement and derivation of averaged pressure across the selected sensors in each region: the velopharynx, meso-hypopharynx and UES, as illustrated in Figure 4.3. They argued that these measurement locations were optimal due to ease in accurate identification of each region: the UES has a clear band of pressure at rest and the velopharynx can be identified by non-swallow speech tasks, such as production of /kaka/ (Takasaki et al., 2008). These anatomic definitions have been used for measurement in numerous subsequent research activities (Hoffman et al., 2010; Knigge et al., 2014; Lin et al., 2014; McCulloch, 2010; Takasaki et al., 2011) and this framework has been adapted in automated analysis programmes described in the literature (Jones, Hoffman, et al., 2014).

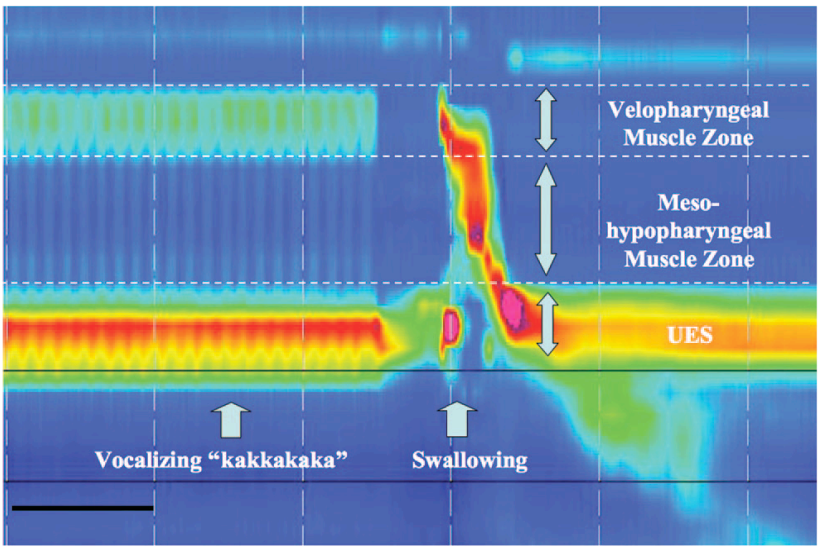


Figure 4.3 This image, from Takasaki et al. (2008)[5], depicts the measurement locations for the three anatomic areas of interest, namely the velopharyngeal region, meso-hypopharynx and UES.

[5] Reprinted with permission of Wiley Publishing (John Wiley & Sons, Inc.).

Importantly, however, the authors did not validate the accuracy of this measurement technique against gold-standard instrumental techniques, such as VFSS. This is critical as recent research has revealed intra-swallow catheter movement contributes to poor identification of anatomic landmarks when compared to VFSS (Jones, Ciucci, Hammer, & McCulloch, 2015). In this study, Jones et al. (2015) aimed to classify sensor movement using simultaneous HRM and fluoroscopy in healthy participants (n=11). Movement associated with UES elevation occurs independent of additional intra-swallow catheter movement related to velopharyngeal closure and 4–6 sensors are needed for interpretation of UES function based on manometric waveforms alone. Further, the authors posit that the optimal location for measurement of nadir UES pressure based on waveforms or topographical plots is unknown (Jones et al., 2015). This is mirrored in a study investigating the reliability of an automated analysis of UES pressure as compared to visual analysis by trained clinicians (Tae Hee Lee et al., 2014). Results indicated there was a poor correlation between measurement of UES relaxation duration between automated software and visual analysis by trained clinicians ($r = 0.29$; 95% CI 0.15 - 0.41). Lee et al. (2014) stated that automated analysis of UES relaxation with HRM is similarly not accurate and called for development of novel analysis techniques. While HRM is the optimal technique for evaluating UES function and overcoming limitations in sensor placement that plague low-resolution manometry, poor reliability in existing analysis techniques limit the utility of this technique.

Difficulties with reliable selection of anatomic areas of interest may be compounded by questionable validity. In the Takasaki et al. (2008) approach, the three anatomic areas, namely the velopharynx, meso-hypopharynx and UES, reduce the high-resolution information garnered from closely-spaced sensors to three averaged points of interest. The results become roughly comparable to output of conventional three-channel manometric systems, which report pressure and temporal data from three similar anatomic areas, namely superior pharynx, inferior pharynx and UES. By averaging across sensors and over time, the numerous publications implementing the Takasaki et al. (2008) method may reduce the specificity of measurement and minimize the advantages of HRM itself. This is critical to consider, especially with ongoing development of pharyngeal HRM automated measurement algorithms.

Most publications rely on software such as MATLAB to analyse pharyngeal swallowing with custom algorithms not distributed with the commercially available instrumentation (Hammer et al., 2009; Hoffman et al., 2012, 2010; C. Jones, Hammer, et al., 2014; Ryu, Park, & Kang, 2015). Reliability of pharyngeal HRM is limited to one study investigating a custom MATLAB programme. Jones et al. (2014) evaluated the reliability of a custom-built software programme when used by 20 raters with varying experience (e.g., expert and novice speech-language pathologists) after provision of a 20-min training session. Raters analysed 30 high-resolution manometry plots. The external analysis programme performed with moderate to high inter-rater reliability (ICC = 0.54-0.99) and intra-rater reliability (ICC = 0.67-1.00) across all experience levels. However, clinical users of pharyngeal HRM are unable to access these custom technologies and are currently reliant on evaluation of swallowing with system-based technologies.

Lastly, HRM is limited by a measurement error that has been reported in the ManoScan™ system (Babaei, Lin, Szabo, & Massey, 2015; Robertson et al., 2012). Though it is unclear if this measurement error occurs in other devices, the ManoScan™ system is used widely in research (Hammer et al., 2009; Hoffman et al., 2012; Jones et al., 2015; Knigge et al., 2014; Lee et al., 2014; Mielens et al., 2012; Nativ-Zeltzer et al., 2012; O'Rourke et al., 2014; Takasaki et al., 2011). A pressure drift has been found to refute the manufacturer's report that pressure uniformity remains within 2 mmHg for 4 or less hours of recording (Babaei, Lin, et al., 2015; Robertson et al., 2012). ManoScan™ provides a standard correction method in the analysis software. This correction, termed thermal correction (TC), is a single-step process where the user applies the correction method at a manually selected time point following extubation - while the catheter remains at body temperature, but with no external pressure applied. The recorded pressure on each sensor at this time point immediately post-extubation is then subtracted from the entire recording from each respective sensor to remove this temperature-related measurement error (Robertson et al., 2012).

However, an additional measurement error, consisting of an increased pressure drift over time, has also been reported (Robertson et al., 2012). Notably, there is no standard correction for this error in the ManoScan™ manual and the standard TC process does not compensate for this increased drift over time (Robertson et al., 2012). The measurement error in the ManoScan™ HRM system is highly variable across sensors and studies and is not corrected

via standard operating instructions (Robertson et al., 2012). This drift can have a substantial impact in clinical diagnosis and research. For example, when evaluating function of UES, normative data indicate that average nadir UES pressure of -4 mmHg has a narrow standard deviation of only 7 mmHg (Mielens et al., 2012). However, previous reports have revealed drift can be as substantial as 11.1 mmHg (IQR 9.9 mmHg) for an average duration study (Robertson et al., 2012), thus caution is needed when interpreting acquired data and forming subsequent diagnoses. While the manufacturer recommends applying TC to all studies prior to analysis, use of TC is only reported in one manuscript (Tae Hee Lee et al., 2014) and the possibility of measurement error and use of standard correction methods were not mentioned in the Knigge et al. (2014) clinical protocol for execution of pharyngeal HRM. This is critical, as it is unclear which results may be affected by measurement error, as overall pressure drift can have a substantial impact in clinical diagnosis and research of pharyngeal and oesophageal function. Thus, further research is indicated to evaluate if this measurement error is an inherent feature of other HRM measurement systems across manufacturers and thus pervasive across this technology.

While it is evident that the advent of high-resolution manometry has overcome many of the limitations of low-resolution pharyngeal manometry, HRM systems are limited by measurement error and as yet poorly established methods for analysis (Robertson et al., 2012). At this point, users of HRM are advised to interpret existing normative HRM data with caution until further studies can replicate data after correcting for measurement error. Long-term, however, HRM will undoubtedly serve an important role in the assessment of pharyngeal swallowing biomechanics, identification of pathologic pharyngeal functioning in patients with swallowing impairment and aid in providing outcome measures for rehabilitation effectiveness.

4.4.3 Impedance

Similar to manometry, intraluminal electrical impedance is commonly used in the field of gastroenterology in functional evaluations of oesophageal motility. In recent years, it has similarly been applied to evaluation of bolus flow in pharyngeal swallowing (Kuo, Holloway, & Nguyen, 2012). The aim of impedance is to monitor both antegrade and retrograde bolus flow in attempts to overcome this limitation of pharyngeal manometry (Kahrilas & Sifrim, 2008). Impedance technology is based on the communication (e.g., current loop) between

adjacent electrodes. These electrodes respond to alterations in conductivity based on the intraluminal environment, such as air, mucosa and bolus (Kahrilas & Sifrim, 2008). A highly conductive ionic bolus (e.g., saline) has low resistance to current flow and can be easily mapped to investigate bolus transfer and residual, if any (Pandolfino, 2009). Thus, "impedance allows for inferences to be made about the relationship between abnormalities of motility seen on manometry with the abnormalities in bolus transit seen on impedance" (Kuo et al., 2012, p. 27). The impedance sensors are typically distributed between the manometric pressure sensors in combined systems. For example, there are a total of 18 channels at 20 mm intervals in the ManoScan™ System. These high-resolution impedance systems enable continuous visualization of the bolus when in contact with adjacent electrodes during transit or at rest (Pandolfino, 2009).

Much of the research in impedance is conducted in reference to oesophageal swallowing. However, select research groups have investigated application of this method to pharyngeal swallowing. Omari et al. investigated analysis methods of impedance-manometry data, combining manometric evaluations of swallowing to generate a gestalt measure they argue may circumvent the need for VFSS in clinics with limited access or in patients difficult to evaluate due to mobility or cognitive deficits (Omari, Dejaeger, Tack, Van Beckevoort, & Rommel, 2013). By comparing the relationship between impedance (bolus flow) and pressure, their methodology enables computation of 'pressure flow' related measures, most notably the Swallow Risk Index (SRI). The SRI compares four pressure and flow variables to compute an overall risk index (Omari et al., 2011). In two studies investigating adult and paediatric patients with dysphagia (n = 43) and healthy controls (n= 10), they determined an SRI cut-off of 9 could predict pharyngeal residue with moderate sensitivity (75%) and specificity (80%). Further, they reported an SRI cut-off score of 15 correlated well with aspiration observed on VFSS (r = 0.85; Omari et al., 2012; Omari et al., 2011). This has been expanded into their Automated Impedance Manometry (AIM) analysis, a custom MATLAB-based software programme designed for the user to interpret pressure flow analyses based on a standard protocol (Omari et al., 2013). The AIM analysis software has been found to have high mean inter-rater (ICC = 0.91) and intra-rater (ICC = 0.97) reliability (Omari et al., 2011; Szczesniak et al., 2015) but it is not currently available for clinical use.

Although these advances have aided in the translation of research of impedance to utilization of this technique in clinical practice, it should be noted that impedance is an estimate of bolus flow based on conduction. Therefore, there are limitations. For example, residual bolus material spanning just one sensor, unable to fulfil the circuit loop of two adjacent sensors, will not be reflected in the impedance measures. Further, prior work in oesophageal swallowing has indicated that impedance has reduced ability to detect small liquid quantities and increased sensitivity to catheter movement, similar to manometry (van Wijk et al., 2009). It is also difficult to quantify the percent or quantity of bolus material ingested with impedance flow analysis. Comparable to the limitations of bolus residual estimations in two-dimensional VFSS, an impedance signal depicts presence of residual, without capability to quantify specific amount. Thus, using the impedance technology as a screening measure of bolus flow may be appropriate, until further developments in standardized analysis programmes (e.g., AIM analysis) can be undertaken.

Impedance has been hailed as a correlate, and even surrogate, to VFSS (Lee et al., 2014). However, it is critical to note that analysis of bolus flow is not the sole purpose of completing a VFSS. With a thorough VFSS, the clinician can not only diagnosis impairments in functional biomechanics and airway protection, but also generate compensatory and rehabilitation targets. This far surpasses the capabilities of impedance technology. Nevertheless, impedance may serve as an adjunct tool for follow-up and outcome assessments, limiting exposure to radiation. With further knowledge of benchmark normative data and standardized analysis methods relevant to pharyngeal swallowing, this technique may prove beneficial as an adjunct screening method for impairments in bolus transit during deglutition. Lastly, its' portability and capability for use in paediatrics add great value to clinical practice. Further research is needed to strengthen the normative database and a standard bolus preparation and administration protocol is needed to ensure uniform analysis of impedance data.

Chapter 5: Dysphagia

Dysphagia is a significant morbidity associated with aging, neurologic impairment, congenital disorders and traumatic injury (Clavé & Shaker, 2015). In some cases, dysphagia presents as nothing more than coughing during meals. In other cases, the disorder is so profound it limits eating entirely, requiring patients to be fed through a gastric tube. In addition to the social isolation that frequently follows, the development of aspiration pneumonia as a result of a swallowing impairment is a grave concern and can result in loss of life at the patient level and enormous financial costs at a systems level. To estimate the impact of dysphagia relevant to New Zealand, there are over 6,000 new stroke events each year with 3,000 of those patients estimated to present with dysphagia (Stroke Foundation of New Zealand, 2009). This contributes to an annual lifetime cost of stroke estimated at $450 million (Stroke Foundation of New Zealand, 2009). With a rising stroke incidence in Māori and Pacific Island populations by up to 66% across a 20-year period, there is a parallel reduction in the age of onset of neurologic impairment that can lead to dysphagia in these populations, 10-15 years earlier on average (Feigin, McNaughton, & Dyall, 2007; McNaughton et al., 2011). This contributes to a longer lifetime of disability for those who survive at great expense for the health sector. Thus, detailed understandings of epidemiology and pathophysiology of this disorder are paramount to promote best practice in rehabilitation and avoid negative secondary outcomes associated with dysphagia.

5.1 Incidence and prevalence of dysphagia

To accurately understand the incidence and prevalence of acquired dysphagia across individuals, it is paramount to consider the analysis method (Clavé & Shaker, 2015). For example, in acute stroke, screening ranks the prevalence of dysphagia between 37–45%, while instrumental examination increases the prevalence to 64–78% (Martino et al., 2005). This is paralleled in chronic stroke, with clinical examinations reporting a prevalence rate between 25–45%, increasing to 40–81% when instrumental examination is conducted (Martino et al., 2005). In PD, differences in prevalence can relate to patient awareness of deficits. For example, patient reports of dysphagia have been found to be 35% while instrumental exploration raises the prevalence to 82% (Kalf, de Swart, Bloem, & Munneke, 2012). A similar pattern is found in dementia. While cognitive-communication deficits in this group may render patient report unreliable, caregivers rating of dysphagia are often relied

upon. However, caregiver report of presence of dysphagia was found to be 19%, markedly lower than the 57% based on instrumental examination in the same patients with dementia (Langmore et al., 2007).

Despite this variability in measurement, it is clear that oropharyngeal dysphagia is experienced widely. Adult patients are typically partitioned into cohorts consisting of those with age-related changes such as sarcopenia contributing to decline, patients with neurologic impairment, and those with acquired anatomic/structural impairment, seen in head and neck cancer. However, these cohorts can overlap in patients with multiple comorbidities, common in aging patients diagnosed with neurodegenerative disease. Dysphagia has been found to affect up to 30–40% of the population 65 years and older (Sura, Madhavan, Carnaby, & Crary, 2012). While dysphagia can result from sarcopenia and general age-related declines, poly-medicated individuals can suffer from exacerbated symptoms, as sedative and antidepressive medications are associated with dysphagia and xerostomia (Clavé & Shaker, 2015). Age-related increases in dysphagia additionally result from increased risk of neurologic impairment. Degenerative diseases have a higher incidence of dysphagia, 82% in PD patients (Kalf et al., 2012) and 80–100% in advanced stage of amyotrophic lateral sclerosis, dementia and muscular dystrophy (Clavé & Shaker, 2015). With regard to head and neck cancers, prevalence and incidence of dysphagia vary by treatment modality, as the treatment itself can have a profound negative effect on anatomy and integrity of soft tissue structures. For example, up to 44% of patients treated with chemotherapy and radiotherapy develop dysphagia. However, dysphagia typically persists and even worsens, in patients treated with radiotherapy. In a recent analysis, 38.5% of head and neck cancer survivors (n = 122) demonstrated severe, long-term dysphagia, with significant increases in long-term dysphagia in patients with multiple therapies, such as combined chemotherapy and radiotherapy (Caudell et al., 2009).

5.2 Consequences of dysphagia

Dysphagia increases the occurrence of a constellation of associated negative sequelae as well. These complications, including dehydration, malnutrition and pneumonia, can greatly increase risks of mortality (Clavé & Shaker, 2015). The odds of being malnourished are 2.4 times higher among patients with dysphagia (Foley, Martin, Salter, & Teasell, 2009), increasing from 8–28% across acute hospitalization (Rogus-Pulia & Robbins, 2013). Further,

malnutrition is associated with reduced functional status, increased length of stay and poor response to rehabilitation (Cichero & Altman, 2012; Geeganage, Beavan, Ellender, & Bath, 2012). The risk of malnutrition significantly increases in the rehabilitation stage, putting current clinical practices in question (Foley et al., 2009). With malnutrition, dehydration is common in dysphagic patients, with 75% of individuals in long-term care reportedly dehydrated due to recommendation of thickened liquids for dysphagia (Cichero, 2013). Malnutrition and dehydration increase the risk of substantial medical decline, including but not limited to increased fall risk, increased risk of renal failure, impaired mental status and ulceration (Cichero, 2013).

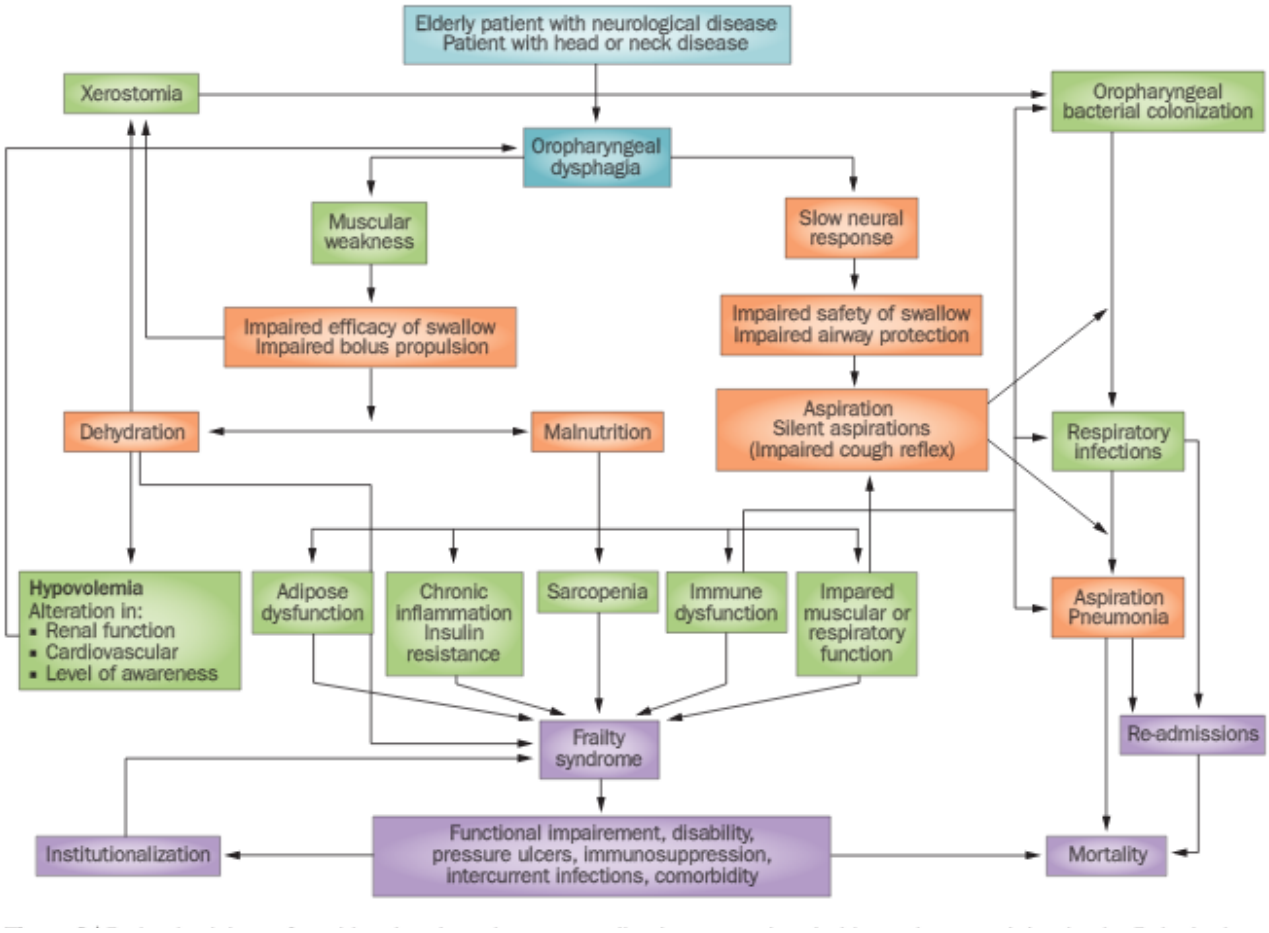


Figure 5.1 Schematic representing the numerous sequelae that can result from oropharyngeal dysphagia. Swallowing function is intimately connected with medical status, as infections contributing to a decline in mental function, for example, can both cause dysphagia and be a symptom resulting from dysphagia (Clavé et al., 2016).[6]

[6] Reprinted by permission from Macmillan Publishers Ltd: Clavé, P., & Shaker, R. (2015). Dysphagia: current reality and scope of the problem. Nature Reviews. Gastroenterology & Hepatology, 12(5), 259–70), copyright (2016).

Aspiration pneumonia is highly associated with dysphagia and is the main cause of death in patients with degenerative diseases such as PD and dementia (Clavé & Shaker, 2015). Patients who aspirate any amount or consistency on VFSS have a 7.6 times greater odds ratio for developing aspiration pneumonia (Schmidt et al., 1994). Aspiration of food/fluid into the lungs during acute admission produces an odds ratio for death of 4.4 (Power et al., 2009). Further, the incidence of dying secondary to aspiration pneumonia has been identified at 5%, or 12,000 deaths per year in the United States (Chang et al., 2013). This is summarized in a review of hospitalization rates in a large epidemiological study (n = 273,141). Baine et al. (2001) found patients diagnosed with aspiration pneumonia nearly doubled over an 8 yr period, with admission for aspiration pneumonia associated with the a 23.1% increase in fatality rate compared to similar patients without a diagnosis of aspiration pneumonia (Baine, Yu, & Summe, 2001).

Dysphagia also contributes to a notable decline in quality of life (Clavé & Shaker, 2015). Ekberg et al. (2002) reported 41% of a large patient cohort (n = 360) reported anxiety and panic during mealtimes, with 36% of patients refusing to eat with others due to their swallowing impairment (Ekberg, Hamdy, Woisard, Wuttge-Hannig, & Ortega, 2002). This can be exacerbated in younger patients, who demonstrate pronounced reduction in quality of life due to long-term impairment in supporting a family, engaging in a career and interacting effectively in a social context (Desrosiers, Noreau, Rochette, Bravo, & Boutin, 2002; Dijkerman, Wood, & Hewer, 1996). Studies have shown younger individuals additionally experience worsened self-rated global health, with increased incidence of impairment in mobility, self-care and depression (Palmcrantz, Widén Holmqvist, & Sommerfeld, 2014).

5.3 Pathophysiology of dysphagia

Swallowing impairments can arise from central and peripheral nervous system damage, affecting any or all phases of swallowing. Further, dysphagia can result from impairment in associated systems such as respiration and due to a variety of causes, including but not limited to tumours, diverticulum and defects from treatment such as radiation or surgical resections (Clavé & Shaker, 2015; Sura et al., 2012). Patients can present with marked impairments in airway protective mechanisms and specific neurologic conditions can predispose patients to common clusters of impairment. For example, in PD, patients are likely to present with impaired bolus transport, lingual incoordination and impaired UES relaxation,

with associated increased risk of aspiration (Ali et al., 1996). This contrasts to a vastly different presentation seen, for example, in patients with chronic obstructive pulmonary disease. Although they may have no structural or neurologic origin for their dysphagia, patients with this disease may continue to be predisposed to an increased risk of aspiration due to shortness of breath and increased frequency of swallowing occurring mid-inspiration (Clavé & Shaker, 2015).

Sensory impairments are often overlooked in the evaluation of dysphagia (Steele & Miller, 2010). This may reflect difficulty identifying sensory impairments, both by clinicians and from patient report. For example, Scharitzer et al. (2002) reported that of more than 3,000 patients undergoing VFSS for evaluation of pharyngeal dysphagia, 14% (n = 434) presented with primarily oesophageal impairment, despite complaints of pharyngeal dysphagia and globus (Scharitzer et al., 2002). In contrast, clinical bedside evaluation identified only 18% of patients (n = 43) who presented with silent aspiration during VFSS (Splaingard et al., 1988). Sensory impairment can have a pronounced impact on swallowing integrity, with aspiration linked to dramatic worsening of health outcomes, as discussed above (Clavé & Shaker, 2015).

Lastly, current understanding of pathophysiologic impairment arises from the type of evaluations clinicians implement. For example, weakness as a primary characteristic of dysphagia is thought to be readily identified on VFSS as the muscles in question visually present with reduced movement and force (Clark et al., 2003; Stierwalt & Youmans, 2007). Importantly, however, a hypertonic muscle would be characterized by rigidity or increased tone causing an inhibition of movement, which may appear similar to the lack of movement seen in weak, hypotonic muscles (Huckabee & Kelly, 2006). Further, recently reported patients with pharyngeal mis-sequencing (Huckabee et al., 2014) present with diffuse pharyngeal residue when swallowing, which is routinely interpreted as a symptom of weakness. However, further investigation with pharyngeal manometry identified mis-sequenced timing of pressure generation in the pharynx, despite relatively normal strength of pressure generation. This finding directly contrasts to the diagnosis of pharyngeal weakness from pharyngeal residual on VFSS. This highlights the limitation of VFSS which only shows movement, not the underlying neurophysiological nature of that movement. Thus, the observation of movement, whether clinical or instrumental, is prone to bias by preconceived

ideas, such as inferences of strength from subjective interpretation of two-dimensional movement on VFSS. Therefore, further research is needed to improve diagnostic classifications and specificity in the evaluation of dysphagia.

5.4 Management of dysphagia

Poor specificity in swallowing evaluation influences subsequent rehabilitation. This is critical, as a misdiagnosed swallowing impairment cannot be treated effectively. For any given treatment, some patients with swallowing impairment may not respond with improved function, suggesting error in the specificity of diagnosis and treatment in many cases. This is coupled with the fact that some presentations of dysphagia currently have no treatment options (e.g., silent aspiration) and some patients may not be rehabilitation candidates due to the severity of their neurologic damage. However, given our rudimentary classification system of pathology in dysphagia (e.g., weakness), this is understandable. In a recent Cochrane review which evaluated 33 studies (n = 6,779), Geeganage et al. (2012) reported "there remains insufficient data on the effect of swallowing therapy, feeding and nutritional and fluid supplementation on functional outcome and death in dysphagic patients with acute or subacute stroke" (p. 2). What is known, however, is that successful rehabilitation is imperative (McNaughton et al., 2014). Research indicates that patients who are reliant on alternate routes for nutrition and hydration (e.g., feeding tubes) at discharge from inpatient rehabilitation have increased risk of mortality at follow-up compared to those patients eating an oral diet or had no signs of aspiration on VSS (Ickenstein et al., 2005).

Compensatory management provides temporarily improved safety or efficiency of oral intake of food and fluid, with benefits eliminated if the compensatory strategy is not implemented. Such strategies include postural modification, such as head turn (McCulloch, 2010) or chin tuck (Ashford et al., 2009), swallowing manoeuvres, including supraglottic swallow (Bülow et al., 2001) and modified bolus textures through manipulation of food texture and fluid viscosity (Cichero, 2013). Compensation typically centres around fluid and diet modification, with thickened liquids reported to be one of the most frequently used compensatory strategies in dysphagia management despite conflicting evidence (Sura et al., 2012). While this may be unavoidable in patients unsuitable for behavioural rehabilitation, such as those with severe cognitive-communication impairments, modification of bolus textures has been associated with poorer outcomes, beyond the negative outcomes associated with dysphagia. Numerous

studies have identified poor patient compliance with thickened liquid, increasing the risk of dehydration in patients (Garcia, Chambers, & Molander, 2005; Sura et al., 2012; Whelan, 2001). Further, aspiration of thickened liquids in a rabbit model was linked to a significantly greater mortality. Only 12.5% of 24 animals survived 3 days of 1.5 mL induced aspiration of thickened liquid, compared to 100% survival of rabbits who were induced to aspirate thin liquid water (Domer et al., 2014). The widespread use of thickeners contrasts to the limited evidence for their efficacy (Cichero, 2013). To complicate matters, there are no universally agreed upon clinical guidelines for solid food texture modification and the consistencies used in instrumental examinations may not reflect textures ingested at mealtimes (Steele, Van Lieshout, & Goff, 2003). This has substantial clinical ramifications. In a study of diet levels of nursing home residents (n = 212), 91% of residents were placed on overly restrictive diets and 4% were at unsafe dietary levels (Groher & McKaig, 1995). Therefore, recommendations for compensatory approaches should be made with consideration of dehydration and compliance, with the awareness that compensation should be a short-term approach in anticipation of long-term rehabilitation.

Rehabilitation for oropharyngeal dysphagia aims to improve impaired swallowing biomechanics. Historically, swallowing rehabilitation has centred on muscle strengthening paradigms. Such exercises include oral motor exercises (Hägg & Anniko, 2008), head-lift exercises (Shaker et al., 2002), expiratory muscle strength training (Troche et al., 2010) and Mendelsohn manoeuvre (Wheeler-Hegland, Rosenbek, & Sapienza, 2008). However, adverse effects have been reported with strengthening exercises, such as effortful swallowing (Garcia, Hakel, & Lazarus, 2004) and current research is highlighting improvements based on skill, rather than strength, training (Athukorala et al., 2014; Humbert & German, 2013). Despite the rehabilitation paradigm used, biofeedback likely plays a critical role in the ability to maximize cortical capacity to modulate aspects of pharyngeal swallowing (Groher, 2000; Humbert & Joel, 2012; Lamvik, Jones, Sauer, Erfmann, & Huckabee, 2015). However, this type of behavioural rehabilitation is limited by understanding of swallowing neural control. With advancements in research, further understanding of novel techniques to support neural plasticity such as non-invasive brain stimulation (Macrae et al., 2014), can lead to great progress in the rehabilitation of dysphagia.

There is a pronounced lack of data regarding optimal dose of rehabilitation. However, the fundamental tenets of intensive rehabilitation utilizingthe principles of neural plasticity are supported by rehabilitation research, with reports positive clinical outcomes (Kleim & Jones, 2008; Murray, Ashworth, Forster, & Young, 2003; Robbins et al., 2008). A systematic review revealed intensive multidisciplinary rehabilitation was associated with reduced odds of mortality (odds ratio, 0.66), institutionalization (odds ratio, 0.70) and dependency (odds ratio, 0.65; Langhorne & Duncan, 2001). Despite this evidence, McNaughton et al. (2014) revealed only 50% of rehabilitation units in New Zealand and 51% of rehabilitation units in Australia achieved 1 hour per weekday of direct therapist-patient contact time and stated "few services in New Zealand provide community or outpatient rehabilitation more than 2 or 3 days per week" (McNaughton, McRae, Green, Abernethy, & Gommans, 2014; p.17). This is in stark contrast to evidence-based recommendations for rehabilitation to have a minimum intensity of 45 minutes per day, for each discipline.

It is paramount to continue rehabilitation in chronic patients. Animal studies have shown that neural plasticity can continue to occur via active practice, even after the spontaneous recovery process has been thought to have ended (Whitall, McCombe Waller, Silver, & Macko, 2000). Miyai et al. (1998) found significant functional gains in chronic stroke patients even when multidisciplinary rehabilitation intervention was commenced after 90 days post stroke. Similarly, in a meta-analysis investigating benefits of rehabilitative services as compared to medical care alone, Evans et al. (1995) found that patients who received multidisciplinary management had significantly better odds of survival and increased functional capacity, with improved likelihood of returning to work. Importantly, however, these gains were not maintained at 8–12 mo after discharge from treatment, indicating a critical need for continued rehabilitation in the chronic phases to maintain gains and further promote recovery (Evans, Connis, Hendricks, & Haselkorn, 1995).

5.5 State of Practice

In order to optimise best practice with regard to the evaluation and rehabilitation of dysphagia, a clear understanding of the state of practice is needed, with full comprehension of gaps in our knowledge and clinical methodology. For example, broader understanding of unique patient presentations, such as those with pharyngeal mis-sequencing, are difficult as many temporal parameters of pharyngeal swallowing are not easily observable on routinely

used instrumental assessments due to inadequate temporal resolution. However, pharyngeal mis-sequencing is readily detected using manometry. Yet, this technique has had limited clinical application with an absence of reliability and validity data relating to its use. This needs to be explored further.

Therefore, in the subsequent chapter, the aims and hypotheses for this thesis will be summarized. Though the studies included in this thesis appear disparate, our questions arise from execution of behavioural studies that have revealed notable methodological limitations affecting best research and best practice. It quickly became apparent that existing diagnostic methods used in studies evaluating central control of swallowing might be inadequate for understanding this rapid sensorimotor response. Other techniques such as low-resolution manometry are not commonly utilized in clinical practice and recent advancements with the development of HRM have not been evaluated in terms of reliability and validity. Thus, the present research programme provides directives for increasing and refining the use of more sensitive and robust instrumental techniques in comprehensive diagnostic evaluation of dysphagia. With this understanding, future studies can contribute to shortcomings in the literature regarding volitional modulation and the nature of underlying neural control of pharyngeal swallowing and improve the state of practice in dysphagia.

Chapter 6: Objectives and Hypotheses

6.1 Behavioural Studies

6.1.1 Incidence, Aetiology and Pathophysiology of Pharyngeal Mis-sequencing in Dysphagic Patients with Neurologic Impairment

Research question: Recent clinical experience has identified a group of patients presenting with an atypical and sometimes profound dysphagia characterized by mis-sequenced pharyngeal pressure when swallowing (Huckabee et al., 2014). The incidence and natural history of pharyngeal mis-sequencing in patients with neurological disorders was not known. What were the defining characteristics of pharyngeal mis-sequencing and in which cohort(s) of neurologic impairment is pharyngeal mis-sequencing observed? Was the temporal development of pharyngeal mis-sequencing the same across cohorts, or variable between or within cohorts?

Objective: To observe the incidence and pattern of development of pharyngeal mis-sequencing with pharyngeal manometry in patients with cortical stroke, brainstem stroke, PD and base-of-skull surgery.

Hypothesis: Two plausible, yet contrasting, hypotheses could be justified by existing knowledge. If pharyngeal mis-sequencing was a result of direct neurologic deficit itself, it was hypothesized that pharyngeal mis-sequencing would be evident at the initial and subsequent data collection sessions in patients with brainstem stroke and base-of-skull surgery which directly affect neural structures responsible for swallowing motor programming. It would not expected to see mis-sequencing in the cortical stroke or PD groups. Conversely, if pharyngeal mis-sequencing was a consequence of a maladaptive response to chronic dysphagia, it was hypothesized pharyngeal mis-sequencing would be evident in all patients with swallowing impairment, irrespective of aetiology, at the 3- and 6-month data collection sessions, with no evidence of mis-sequencing immediately post-onset.

Significance: A prospective incidence study was needed to not only further identify specific patient groups who exhibit pharyngeal mis-sequencing, but also to explore the patterns of development of pharyngeal sequencing itself. Pharyngeal mis-sequencing in dysphagia was not easily observable on VFSS. Therefore, this project would provide important information

to encourage the use of more accurate diagnostic tools, such as pharyngeal manometry, in appropriate patients to prevent misdiagnosis of swallowing problems. Further, this this study was needed to provide researchers a full report of pharyngeal mis-sequencing, detailing much needed information regarding the nature of underlying neural control of swallowing. Thus, the results of this project would likely translate immediately to improved patient care and greater scientific understanding of the complex neural control of swallowing.

Proposed Study (see Chapter 7): The pilot study evaluated patients with dysphagia as a sequela of four brain disorders (n = 7): base-of-skull surgery, brainstem stroke, cortical stroke and PD. This represents initial data from a larger, ongoing study recruiting a larger sample of the same cohorts (n = 100). Their swallowing was evaluated with manofluoroscopy, combined VFSS and pharyngeal manometry. Each subject was asked to perform 5 dry swallows, three 10 ml liquid trials and three 10 ml puree trials. Follow-up evaluations were completed at 1, 3 and 6 months post-onset (see section 7.2.3 for further details).

6.1.2 Volitional Control of Pharyngeal Swallowing in Healthy Adults

Research question: Previous research has documented that pressure and duration of brainstem-generated pharyngeal swallowing can be cortically modulated (Bülow et al., 2001; Fukuoka et al., 2013; Wheeler-Hegland et al., 2008; Witte et al., 2008). But there was a commonly held belief that the sequence of pharyngeal pressure remains constant (Ertekin, 2011). It was unclear to what capacity of healthy humans can volitionally alter the 'reflexive' components of the pharyngeal swallow.

Objective: To examine if healthy adults could volitionally produce altered latency of pharyngeal closure in isolation following intensive training using pharyngeal manometry as visual biofeedback, thereby evaluating the capacity for pharyngeal adaptation in a healthy system.

Hypothesis: Normal healthy adults would be able to adopt a motor plan which recruits pharyngeal pressure in both the proximal and distal pharynx, with substantially reduced peak-to-peak separation between pharyngeal manometric sensors following two weeks of daily biofeedback training. This would be accomplished without a simultaneous reduction in total swallowing duration, suggesting that the adaptation was one of volitional temporal shift of a

specific component of swallowing rather than a more synergistic reduction in overall swallowing duration.

Significance: Successful modulation of the sequence of pharyngeal pressure by cortical voluntary mechanisms would provide evidence to challenge the assumption that the sequence of pharyngeal pressure generation is a fixed and patterned reflexive response, unable to be cortically modulated. The ability to gain volitional modulatory control over targeted aspects of the pharyngeal swallow may serve an important avenue for rehabilitative treatment.

Proposed Study (see Chapter 8): Participants were seen for intensive training with the goal of producing simultaneous pharyngeal pressure when swallowing using low-resolution manometry as a visual biofeedback modality. The temporal separation of peak proximal and distal pharyngeal pressure at baseline, during training with biofeedback and following training without biofeedback were compared with Friedman's tests and post-hoc pair-wise comparisons with Wilcoxon signed-rank test (see section 8.2.3 for further details).

6.1.3 Pharyngeal Swallowing during Wake and Sleep States

Research question: Sleep has been associated with stages of relative cortical quiescence (Orr, Heading, Johnson, & Kryger, 2004), enabling evaluation of swallowing under periods of reduced volition and awareness (Kelly, Huckabee, & Cooke, 2006). What were the biomechanical characteristics of reflexive pharyngeal swallowing in humans?

Objective: To evaluate parameters of reflexive pharyngeal swallowing responses during sleep, which would inform on the role of volition and arousal in control of pharyngeal swallowing.

Hypothesis: It was hypothesized that normal healthy adults and patients with dysphagia would demonstrate a significant difference between baseline and sleep swallow parameters as measured by HRM, with shorter total pharyngeal duration and lower amplitude when asleep. Further, the latency between maximal superior and inferior pharyngeal pressure would be significantly reduced during sleep as compared to wake states.

Significance: This was the first study to compare pharyngeal pressure during sleep with wake conditions in healthy adults and patients with dysphagia using manometry. Changes in pharyngeal pressure measures when asleep, as compared to wake states, would suggest a significant role of cortical modulation of the pharyngeal swallowing response. This may provide additional data regarding the debate or the role of volition in swallowing motor control. This was of interest when considering understanding of pharyngeal swallowing and development of novel rehabilitation protocols.

Proposed Study (see Chapter 9): Pharyngeal swallowing was evaluated with pharyngeal HRM in wake upright, wake supine and sleep conditions. Slope and latency of superior-to-inferior pharyngeal pressure, as well as maximal amplitude of pharyngeal pressure, were analysed. Comparisons were made between the three sleep and two wake conditions using paired t-tests and one-way analysis of variance with post hoc testing (see section 9.2.3 for further details).

6.2 Methodological Studies

6.2.1 A Comparison of Low- and High-resolution Pharyngeal Manometry

Research question: The advent of HRM overcame many of the limitations of low-resolution manometry. However, there was a discrepancy in the literature when comparing normative pharyngeal pressure data, with variable temporal data and markedly increased standard deviations using HRM instrumentation (Lamvik et al., 2014; Mielens et al., 2012). How do low- and high-resolution manometry compare in a within-subject investigation of amplitude and latency of pharyngeal pressure?

Objective: To evaluate timing and amplitude of swallowing pressure by comparing two methods of recording pharyngeal pressure generation: unidirectional, low-resolution manometry and circumferential, high-resolution manometry.

Hypothesis: There would be no significant difference in the peak or nadir amplitude between the two sensor types. There would be no significant difference in the duration of UES relaxation.

Significance: Advancements in the development of HRM have largely replaced a long history of manometric data collected with standardized, unidirectional low-resolution catheters. Understanding differences in measurement between these two intraluminal pressure measurement devices was critical to explain the variability in normative data collected by these instruments. This may aid in improving diagnostic specificity.

Proposed Study (see Chapter 11): Low- and high-resolution manometry measurements were investigated using a within-subject design, with order of evaluation equal across two counter-balanced groups. Participants were evaluated under four conditions with low-resolution manometry, specifically with the unidirectional sensors recording in one of four directions intraluminally to mimic circumferential evaluation. In each condition, the participant performed five dry swallows and five 10 mL liquid bolus swallows. During HRM, participants performed the same protocol of ingestion, including dry and liquid swallows in one recording condition. Amplitude and latency of pressure were directly compared in corresponding sensors within each participant and across conditions with repeat-measures ANOVA (see section 11.2.3 for further details).

6.2.2 Characterization and Correction of Measurement Error in Low- and High-resolution Manometry: In-Vitro and In-Vivo

Research question: Valid investigation of timing and amplitude of pharyngeal pressure is reliant on instrumental measurement accuracy. However, a substantial pressure drift in the ManoScan™ HRM system has been reported (Babaei et al., 2015; Robertson et al., 2012) and similar investigations of measurement consistency in low-resolution manometry are not evident in the literature. What measurement error is evidenced pharyngeal manometry and with what accuracy do possible error corrections perform?

Objective: To explore measurement error and subsequent compensation with low-resolution manometry and HRM in-vitro and in-vivo, in both abbreviated and extended-length recordings.

Hypothesis: Due to the differences in sensor composition, measurement would be consistently uniform in extended duration low-resolution manometry studies. However, a

significant measurement error would be documented in HRM. It is hypothesized the available correction methods will appropriately compensate for the measurement error.

Significance: This study was the first to analyse possible measurement error both in-vitro and in-vivo in low- and high-resolution manometry. Controlled in-vitro studies are robust for investigating system faults and comparison to in-vivo data was critical for both clinical use and future research of HRM. Thus, identification and characterisation of measurement error in pharyngeal manometry can have a substantial impact in clinical diagnosis and utility of existing normative data.

Proposed Study (see Chapter 12): Short and extended duration studies were completed with low-resolution manometry and HRM. Studies were performed in-vitro using a water bath at 37°C and in-vivo studies will be performed with healthy participants. Two correction methods – TC and interpolated thermal compensation (ITC) – were tested (see section 12.2.3 for further details).

6.2.3 The Effect of Topical Nasal Anaesthetic on Tolerability and Pharyngeal Pressure in Healthy Adults: A Double-Blind Study

Research question: Topical nasal anaesthetic (TNA) is used in research and clinical examinations with pharyngeal HRM and recommended in clinical HRM protocols (Knigge et al., 2013). However, it was unclear if desensitizing the nasal mucosa improves procedure tolerability or affects pharyngeal swallowing.

Objective: To evaluate the effect of TNA on participant perception of procedure comfort, as well as timing and amplitude of pharyngeal swallowing using pharyngeal HRM.

Hypothesis: There would be no significant differences in the participant report of procedure comfort between the two TNA and placebo test conditions. Further, healthy participants will demonstrate no difference in amplitude and timing of pharyngeal pressure under the TNA and placebo conditions.

Significance: Results from this study may allow refinement of published protocols for conducting this examination and offer further information to guide best practice of pharyngeal HRM and similar trans-nasal intubation techniques.

Proposed Study (see Chapter 13): A double-blind study was conducted with healthy participants, who received two examinations counter-balanced under placebo (lubricant) and anaesthetized (0.4 ml of 2% viscous lidocaine hydrochloride) conditions. Procedural comfort was rated using a 100-mm visual analog scale and comparisons were made using paired samples t-tests (see section 13.2.3 for further details).

6.2.4 Reliability of Clinical Analyses of Swallowing using Pharyngeal High-resolution Manometry

Research question: Knigge et al. (2014) provide the only published clinical protocol for analysis of HRM spatiotemporal plots using existing system-based technologies (e.g., ManoScan™ HRM systems). The reliability of this technique was unknown.

Objective: To evaluate the reliability of clinical swallowing measurements made using the analysis protocol described by Knigge et al. (2014).

Hypothesis: Raters would demonstrate sufficient inter-rater reliability and intra-rater reliability (ICC > 0.75; Portney & Watkins, 2008) consistent with similar prior research (Jones et al., 2014).

Significance: The anatomic and measurement definitions proposed by Knigge et al. (2014) have been used in the majority of pharyngeal HRM studies and are being utilized in ongoing development of automated software programmes (Jones et al., 2015). Therefore, understanding the reliability of this technique is imperative to appreciate the consistency of this system-based measurement for clinical use. This would likely have an impact on diagnostics and best practice, as further research is needed to standardize measurement of pharyngeal swallowing using HRM.

Proposed Study (see Chapter 14): Clinical researchers participated in a 20 min training session for analysing ManoScan™ HRM spatiotemporal plots based on the Knigge et al.

(2014) protocol. Raters analysed 3 individual swallows from 3 healthy participants and 3 patients, with one repeated swallow from each sample for intra-rater analysis. Swallows were coded for blinding and randomized within and across raters. Statistical analysis included ICC to assess intra- and inter-rater reliability, interpreted with Portney et al. (2009) criterion (see section 14.2.3 for further details).

PART II: BEHAVIOURAL STUDIES

Chapter 7: Incidence, Aetiology and Pathophysiology of Pharyngeal Mis-sequencing in Dysphagic Patients with Neurologic Impairment[7]

7.1 Introduction

Clinical experience from University of Canterbury Swallowing Rehabilitation Research Lab has demonstrated a subgroup of patients (n = 16) with atypical pathophysiologic features of dysphagia, profiled in a recent case series (Huckabee et al., 2014). On instrumental examination with VFSS, this patient cohort presents decreased pharyngeal motility, diffuse pharyngeal residue and frequent nasal redirection. Subsequent assessment with pharyngeal manometry reveals a mis-sequenced pattern of pharyngeal pressure, with simultaneous pressure in the proximal and distal pharynx, respectively. The patient cohort was found to have an average peak-to-peak latency between nadir pressures at sensor 1 and sensor 2 of 15 ms (95% CI, -2–33 ms; Huckabee et al., 2014). This is substantially outside on the 95% confidence interval from normative data, which identified a mean latency of 239 ms (95% CI, 215–263 ms) between nadir pressures at sensor 1 and sensor 2 in healthy adults (Lamvik et al., 2014). This pharyngeal mis-sequencing represents essentially simultaneous pressure generation at the level of the proximal and distal pharyngeal regions, as shown in Figure 7.1. Further, total swallowing duration, defined as the time between the first observed onset of pressure deviation from baseline at any sensor to the last return of pressure to baseline at any sensor, was greater than the normative 95% confidence interval (Lamvik et al., 2014). As a result, the patients were unable to coordinate streamlined food or liquid transfer from the pharynx into the oesophagus, with consequent aspiration, nasal redirection and, for some, inability to tolerate a diet safely by mouth.

[7] Some content from this chapter was published as Huckabee, M-L, Lamvik, K., Jones, R. (2014). Pharyngeal mis-sequencing in dysphagia: Characteristics, rehabilitative response, and etiological speculation. Journal of the Neurological Sciences. 343 (2014), 153-158.

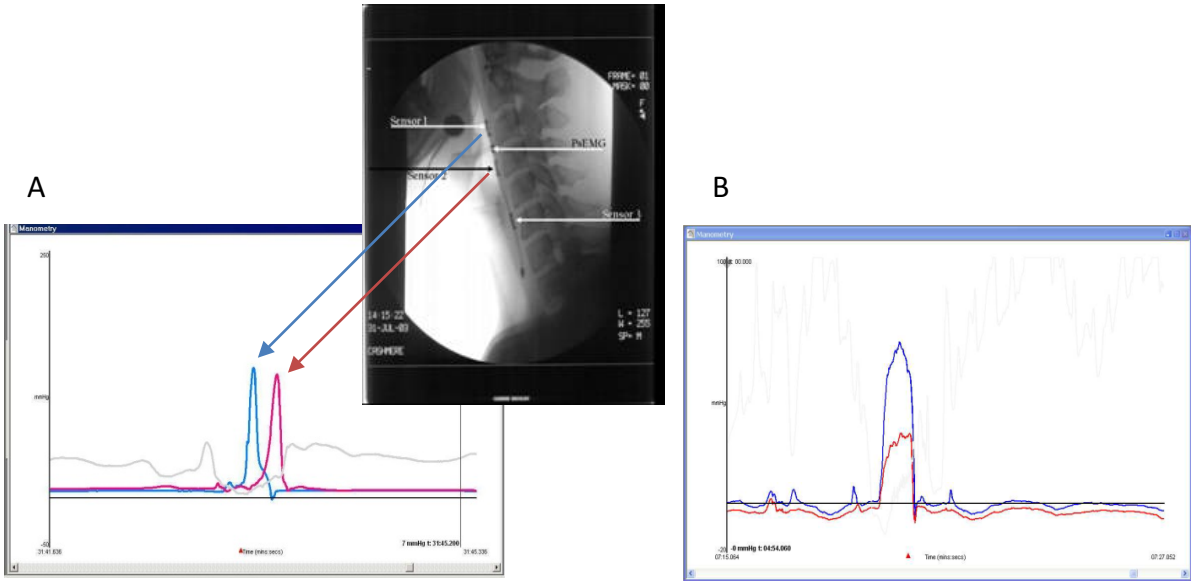


Figure 7.1 Sample manometric waveforms. The blue line is representative of pressure at the level of the base of tongue region and the red line is representative of pressure at the level of the laryngeal additus. The target pattern in Figure 7.1A shows the mean peak-to-peak duration of greater than 200 ms, where, in contrast, the mis-sequenced pattern in Figure 7.1B shows essentially simultaneous pharyngeal pressure generation.

In this group of patients, profound, chronic dysphagia due to pharyngeal mis-sequencing was observed following brainstem stroke and/or base of skull tumour resection. However, dysphagia following base of skull surgery is not commonly reported in the literature, as in the case of pathology resected from the cerebellopontine angle (CPA). The CPA is an anatomic space within the fourth ventricle at the margin of the cerebellum and pons. Tumours in this region account for 8-10% of intracranial tumours and are most frequently acoustic neuromas, although meningiomas, metastases and tumours extending from the cranial base have also been reported (Mallucci, Ward, Carney, O'Donoghue, & Robertson, 1999). Currently, there are only a few retrospective studies that document post-operative dysphagia in this patient population (Best et al., 2012; Jennings, Siroky, & Jackson, 1992; Périé et al., 1999; Ryzenman, Pensak, & Tew, 2004; Starmer et al., 2012). In a large survey of patients (n=1940) following acoustic neuroma surgery, Ryzenman (2004) reported that 31% of patients self-reported dysphagia following their surgery, compared with only 6.5% preoperatively. Similarly, in a retrospective study of 181 consecutive acoustic neuroma patients, Starmer (2012) identified postoperative dysphagia in 31% of patients. VFSS performed in their dysphagic cohort demonstrated pharyngeal residue in 90% of patients and

nasal redirection of the bolus in 18%. Further, 59% of patients demonstrated penetration or aspiration, with 5 documented cases of aspiration pneumonia during the immediate postoperative period from their sample. Manometry was not performed in this study (Starmer et al., 2012). Similarly, Jennings et al. (1992) performed a retrospective analysis of 12 patients who presented with dysphagia following excision of skull base pathology. Via imaging with VFSS, the authors reported frequent observations of reduced laryngeal excursion and copious pharyngeal residue, with aspiration occurring in 75% of the patient group (Jennings et al., 1992).

Pharyngeal mis-sequencing itself is not easily observable on VFSS due to the limits in temporal resolution. In contrast, pharyngeal manometry has substantially greater temporal resolution of pressure changes in the pharynx during a swallow, as discussed in Chapter 4 (Kuo et al., 2012). However, pharyngeal manometry has limited clinical use, with only one study utilizing pharyngeal manometry in the evaluation of base-of-skull surgical patients (Périé et al., 1999). In their study, Périé et al. (1999) performed manofluoroscopy in 7 patients following base of skull surgery, all of whom were referred for evaluation of post-surgical swallowing impairment. They reported findings qualitatively, by assessing pharyngeal propulsion as either 'normal', 'decreased', or 'aperistaltic' from manofluoroscopy. No objective temporal manometric data were reported. However, subjectively stated, the most common feature observed was 'a decrease of pharyngeal propulsion' (Périé et al., 1999).

Pharyngeal mis-sequencing has infrequently been alluded to in other populations. In one study of patients with PD, Ali et al. (1996) used manofluoroscopy to evaluate swallowing function in three groups of participants: PD patients with reported dysphagia (n=12, disease duration average 5.1 years), PD patients without reported dysphagia (n=7, disease duration average 9.1 years) and healthy, age-matched controls (n=23). The authors reported that in 6 of the 12 dysphagic PD patients, there were "synchronous non-propagated mid-pharyngeal and proximal pharyngeal pressure waves" (p. 387). On VFSS, Ali et al. (1996) reported patients presented with diffuse pharyngeal residual following trials. Similar findings were not seen in the PD patients without reported dysphagia or age-matched controls (Ali et al., 1996). Since pharyngeal manometry is infrequently performed and mis-sequencing itself is not

easily observable on VFSS, it is unclear at this time what the true prevalence of pharyngeal mis-sequencing is across populations.

Thus, a prospective, quantitative evaluation of pharyngeal mis-sequencing across patient populations was needed to further identify and characterize this atypical presentation of dysphagia. The aim of this ongoing study was to longitudinally evaluate of a broad neurogenic population (n = 100) to identify the prevalence and pathophysiology of this dysphagic presentation. It was proposed to observe the incidence and pattern of development of pharyngeal mis-sequencing with pharyngeal manofluoroscopy in patients with neurologic impairment by comparing cortical stroke (n = 25), brainstem stroke (n = 25), PD (n = 25) and base-of-skull surgical participants (n = 25). This prospective incidence study might not only further identify specific patient groups who exhibit pharyngeal mis-sequencing, but also to explore the patterns of development of pharyngeal sequencing itself. As this study is still in progress, methods, analysis and discussion reflect data collection completed to date.

7.2 Materials and Methods

7.2.1 Participants

Seven male dysphagic patients have been recruited to date, with an age range of 61–84 yr (average = 74.2 yr). Of the participants, diagnoses include PD (n = 3), cortical stroke (n = 2) and brainstem stroke (n = 2). One cortical stroke patient was unable to be included in analysis due to an error in synchronization of VFSS and manometric data, rendering the manometric data unmeasurable. The brainstem stroke and cortical stroke groups were recruited following referral to a Speech-Language Pathologist for an inpatient VFSS from a medical provider after hospital admission with confirmed stroke. The PD group was recruited following referral to SLP for an inpatient or outpatient VFSS from a medical provider. Therefore, the brainstem stroke, cortical stroke and PD groups presented with dysphagia significant enough to warrant a VFSS. Exclusionary criteria across cohorts included any pre-existing neurologic impairment or history of dysphagia prior to onset of admitting neurologic injury.

7.2.2 Equipment

A 100-cm long, 2.1-mm diameter catheter was used for manometric data collection (Model CTS3 + EMG, Gaeltec, Hackensack, NJ, USA). As per standardized catheter recommendations from Salassa, DeVault, & McConnel (1998), the catheter housed 3 solid-

state, unidirectional, posteriorly-oriented sensors (2 x 5 mm) with 2 cm spacing between sensors 1 and 2, and 3 cm between sensors 2 and 3. Pressures were measured at the proximal pharynx, distal pharynx and UES with sensors 1, 2 and 3 respectively. The catheter was connected to the Kay Elemetrics Digital Swallowing Workstation (Model 7120, Kay Pentax, Lincoln Park, NJ, USA), with digitized recording of pressure waveforms as a function of time displayed in real time in a -100 to 500 mmHg display window on a computer screen and digitally recorded for offline analysis. VFSS was recorded at 25 frames/second, time locked with manometric waveforms on the Kay Elemetrics Digital Swallowing Workstation.

7.2.3 Procedures

Pharyngeal manometry was combined with simultaneous VFSS (e.g., manofluoroscopy). A 2.1-mm diameter catheter was inserted through the nares, with the participant's head at a comfortable resting level. Once the catheter was inserted approximately 10 cm, the participant was asked to raise their chin, allowing for passage of the catheter through the angled velopharyngeal port. After returning head position to normal posture, the participant was then instructed to swallow to 'ingest' the catheter down to the proximal oesophagus (either by ingesting water via straw, or by performing sequential dry swallows). Once the catheter was ingested approximately 30 cm from the tip of the nose, the participant was cued to stop swallowing. A pull–through technique was performed in 5 mm increments. This was continued until correct catheter placement was confirmed through visualization of the typical 'M' wave at sensor 3 during swallowing, corresponding to the superior aspect of the high pressure zone of the UES (Castell & Castell, 1993). Posterior orientation of the three sensors was confirmed by monitoring unidirectional markers on the catheter. When correctly positioned, sensors measured pressure activity at the proximal pharynx approximately at the level of the base of tongue region, the mid-pharynx at approximately the level of the laryngeal additus and the superior aspect of the UES. Catheter placement was evaluated radiographically for correct placement. Once correct placement was achieved, the catheter was taped securely to the external nose with medical adhesive tape.

A radiopaque disk of 2.5 cm diameter was placed on the participants mid-chin to facilitate subsequent data analysis. Prior to oral trials, participants were asked to hold a 1cc bolus in their oral cavity while a still frame was captured (approximately 2 s) to acquire baseline positional data as a reference for subsequent calculations. VFSS were recorded during oral

trials consisting of three dry swallows, three 10 ml liquid boluses and three 10ml puree boluses at 40% w/v ratio of barium sulphate concentration (Varibar Barium Sulfate Contrast, Thin liquid and Pudding, E-Z-EM Canada Inc.).

Data were collected at different intervals across cohorts, due to intrinsic constraints inherent in each group. As stroke is an unplanned event, no pre-stroke data were collected in the brainstem and cortical stroke groups. Additionally, as many cortical stroke patients are lost to follow-up due to cognitive and language deficits, only one planned data collection session was completed, as specified in Table 7.1. PD participants were included at any point in their disease progression and followed longitudinally from the initial data collection session.

Table 7.1 Timeline of data collection for each group.

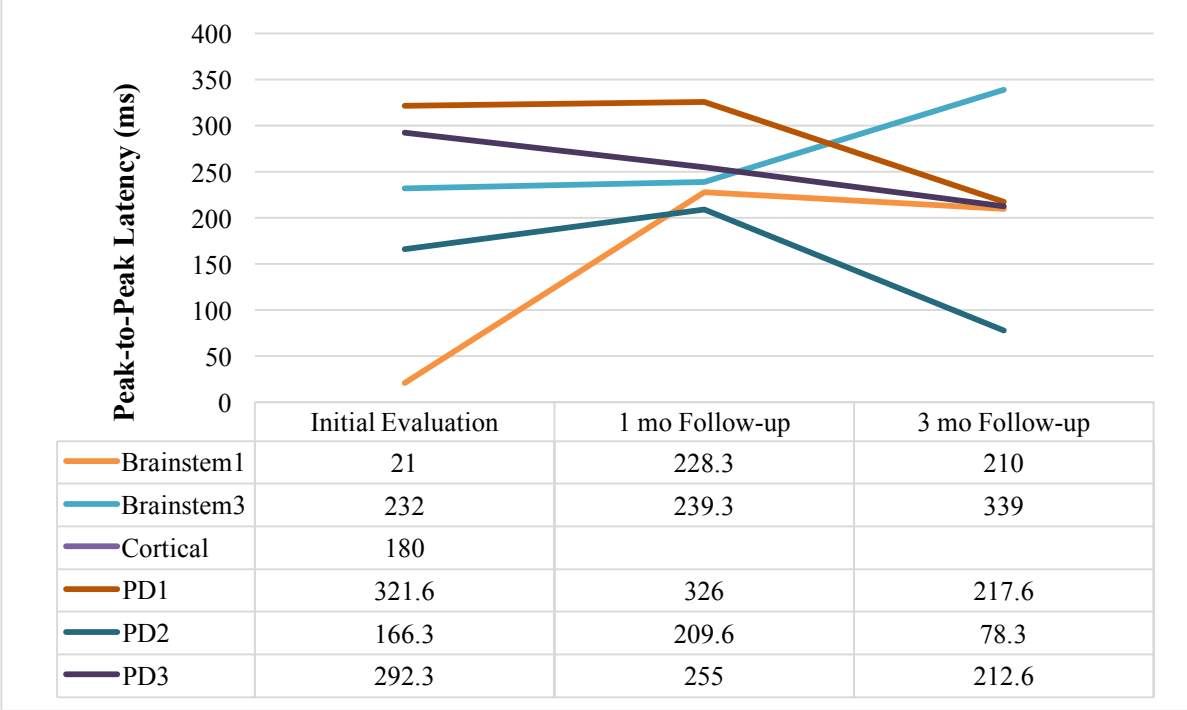
Brainstem Stroke Cohort	Cortical Stroke Cohort	PD Cohort
Evaluation within 1 week following referral for VFSS	Evaluation within 1 week following referral for VFSS	Evaluation within 1 week following referral for VFSS
1 month follow-up		1 month follow-up
3 month follow-up	Follow-up as able	3 month follow-up
6 month follow-up		6 month follow-up

7.2.4 Data Analysis

Pharyngeal pressure generation was measured off-line using the Kay Digital Swallowing Workstation (Model 7120) software with manually placed, digital cursors. Relevant to this study, temporal measures for each swallow were taken to assess peak pressure of sensor 1 to peak pressure of sensor 2, termed peak-to-peak latency (ms). This measure was compared to both normative data (Lamvik et al., 2014) and relevant patient cohorts (Huckabee et al., 2014). Statistical comparisons were not completed for this chapter due to the currently limited number of participants and missing data points. Missing data points were due to technical difficulties in the fourth follow-up session, where an error in the synchronization of VFSS and manometric data rendered the manometric data unmeasurable. Nevertheless, once data collection will be completed across cohorts (n = 100), a mixed effects model will be used to analyse collected data, with cohorts comprising fixed effects and individual participant identifier as random effects.

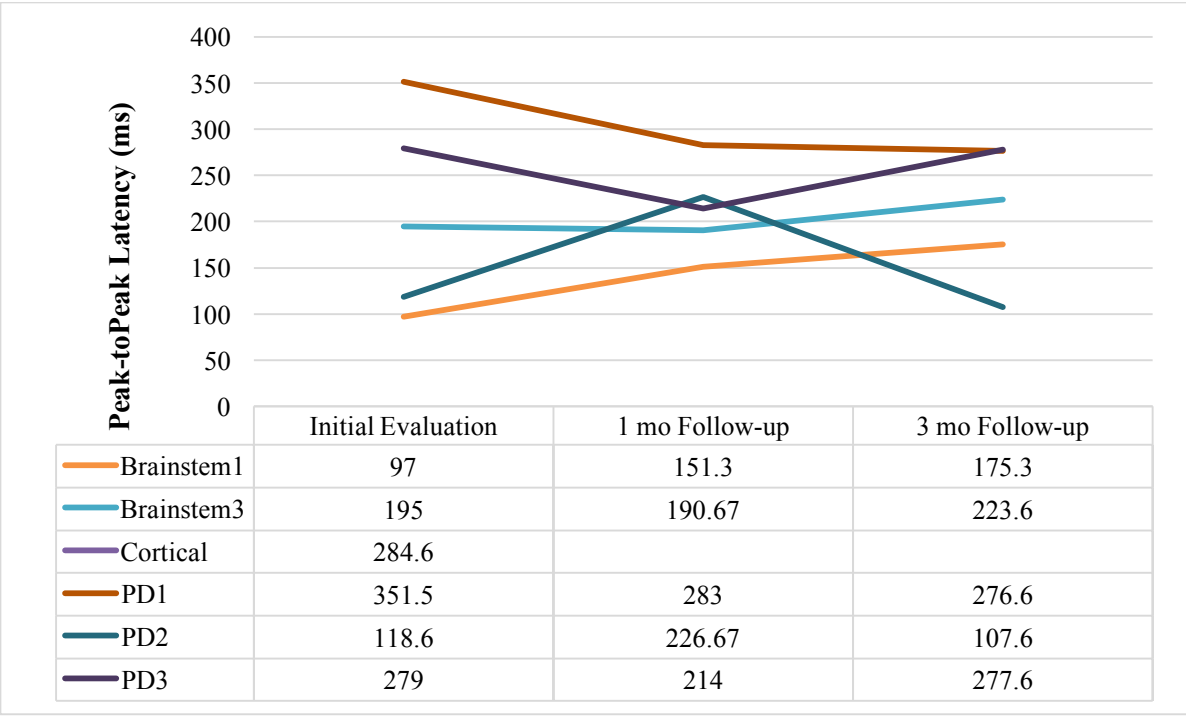
7.3 Results

All participants tolerated the study protocol. Group results revealed dry swallows with a mean average peak-to-peak latency of 221 ms (95% CI = 175–265). This is similar to liquid swallows, with a mean average peak-to-peak latency of 216 ms (95% CI = 176–255) and puree swallows, with a mean of 239 (95% CI, 197 – 280). While the lower bound of 95% confidence interval for the abovementioned values is below normative latency of 239 ms (95% CI = 215–263), it remains above referenced patient values from the Huckabee et al. (2014) cohort (mean = 15 ms, 95% CI = -2–33). Only one measured value was within the 95% confidence interval from the patient cohort, namely the first evaluation session of a patient presenting with brainstem stroke (Figure 7.1). Results from liquid and puree swallows are similarly reported in Figure 7.2 and 7.3, respectively.



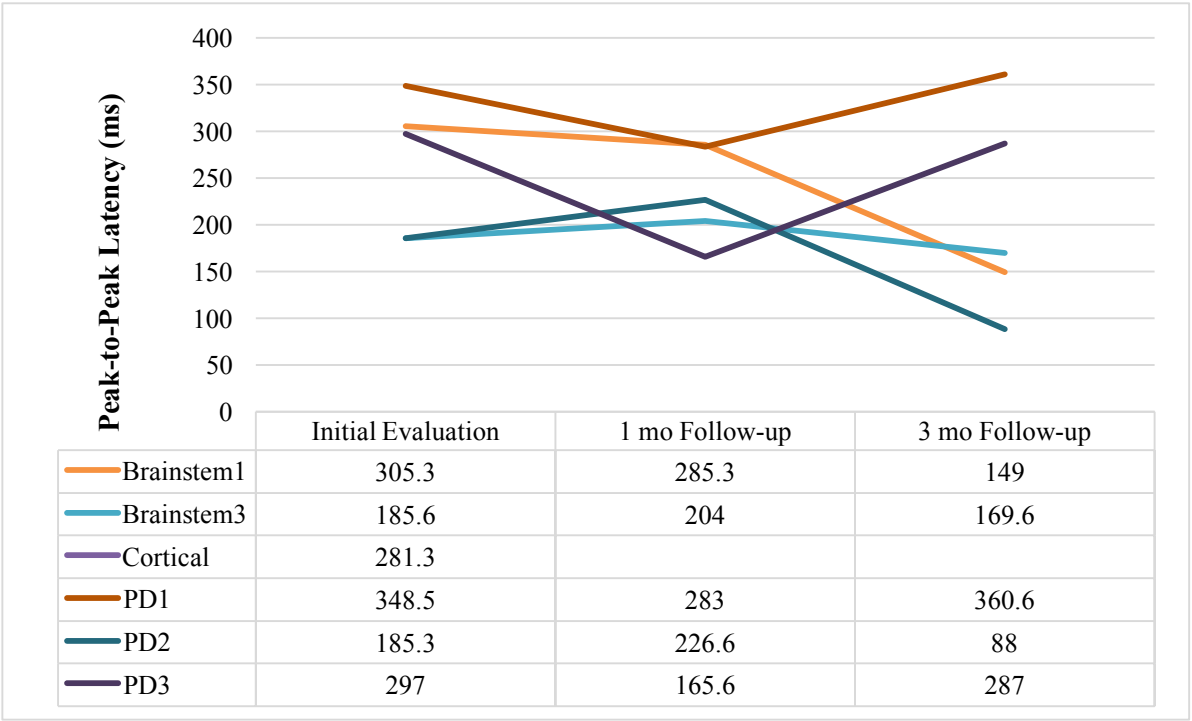
	Initial Evaluation	1 mo Follow-up	3 mo Follow-up
Brainstem1	21	228.3	210
Brainstem3	232	239.3	339
Cortical	180		
PD1	321.6	326	217.6
PD2	166.3	209.6	78.3
PD3	292.3	255	212.6

Figure 7.1 Mean peak-to-peak latencies from the dry swallowing condition across each participant.



	Initial Evaluation	1 mo Follow-up	3 mo Follow-up
Brainstem1	97	151.3	175.3
Brainstem3	195	190.67	223.6
Cortical	284.6		
PD1	351.5	283	276.6
PD2	118.6	226.67	107.6
PD3	279	214	277.6

Figure 7.2 Mean peak-to-peak latencies from the liquid swallowing condition across each participant.



	Initial Evaluation	1 mo Follow-up	3 mo Follow-up
Brainstem1	305.3	285.3	149
Brainstem3	185.6	204	169.6
Cortical	281.3		
PD1	348.5	283	360.6
PD2	185.3	226.6	88
PD3	297	165.6	287

Figure 7.3 Mean peak-to-peak latencies from the puree swallowing condition across each participant.

7.4 Discussion

Due to the limited number of participants recruited, inferences regarding the incidence and pathophysiology of mis-sequencing cannot be posited at this stage. It is worth noting that a patient in the brainstem stroke cohort presented with a peak-to-peak latency within the 95% CI of the mis-sequencing cohort at first evaluation (Huckabee et al., 2014). While averages were not within normative ranges, implying impairment, there is insufficient evidence to date to adequately characterize when peak-to-peak latency becomes pathologic. Nevertheless, while data collection is ongoing, two plausible, yet contrasting, hypotheses can be justified from existing knowledge. It remains unclear if this atypical swallowing impairment is (i) a primary feature of the neurological deficit itself or (ii) a maladaptive compensatory response as a consequence of chronic reduced pharyngeal pressure. If pharyngeal mis-sequencing is a result of direct neurologic deficit itself, it is hypothesized that pharyngeal mis-sequencing will be evident at the initial and subsequent data collection sections in patients with brainstem stroke and base-of-skull surgery which directly affect neural structures responsible for swallowing motor programming. Mis-sequencing would not be expected in the cortical stroke or PD groups. Conversely, if pharyngeal mis-sequencing is a consequence of a maladaptive response to chronic dysphagia, it is hypothesized that pharyngeal mis-sequencing will be evident in all patients with swallowing impairment, irrespective of aetiology, at the 3- and 6-month data collection sessions, with no evidence of mis-sequencing immediately post-onset. While the existing data suggest pharyngeal mis-sequencing may be a result of the neurological impairment itself, both hypotheses are reviewed below.

7.2 Pharyngeal mis-sequencing as a result of neurologic impairment

Currently, published articles theorize that dysphagia following surgical resection of base of skull pathology is a result of cranial nerve damage (Jennings et al., 1992; Périé et al., 1999; Starmer et al., 2012). It has been posited that “given the proximity of the 9th and 10th cranial nerve complex to the CPA, there is also reason to hypothesize that voice and swallowing may be frequently affected by the presence of the tumour itself or by the therapies employed to remove it” (Starmer et al., 2012). Although it is well documented that CPA lesions cause impairment secondary to compression or damage of nearby cranial nerves, including 5th, 7th and 8th, involvement of other cranial nerves, such as vagus, appear to be less common (Ansari, Terry, & Cohen-Gadol, 2012). For example, Zhang (2005) found only 3% of 105 patients were found to demonstrate vagal palsy following surgery (Zhang, Chen, et al., 2005).

Further, in a study investigating outcomes following resection of 'giant' vestibular schwannomas (>4 cm in maximal extrameatal diameter), post-surgical lower cranial nerve dysfunction was observed in only 3 of 50 participants, with complete resolution of cranial nerve damage in all but one patient (Samii, Gerganov, & Samii, 2010). When considering the unique presentation of the cohort presenting with pharyngeal mis-sequencing (Huckabee et al., 2014), it seems unlikely cranial nerve damage alone could account for pharyngeal mis-sequencing, which is a change in the temporal pattern of swallowing, rather than peripheral, lower motor neuron weakness.

It remains unclear why a change in the motor pattern of swallowing would be evidenced in patients with damage to supra-medullary regions, such as the CPA. As stated previously, without damage to the swallowing CPG, the overall motor sequence of the pharyngeal swallow should remain constant, even in the presence of cortical modulation. Therefore, what if our current understanding of central representation of swallowing is inadequate to account for the complexities in human deglutition? Our current understanding of the complex sensory and motor interplay during swallowing has an extensive foundation in animal studies, primarily evaluating dry swallows rather than more complex, ingestive eating behaviour (Amri et al., 1984; Angaut & Bowsher, 1970; Berntson, Potolicchio, & Miller, 1973; Car et al., 1975; Hockman et al., 1979; Jean et al., 1975; Reis, Doba, & Nathan, 2013; Sugiyama et al., 2011). However, considering the unique anatomic and functional differences in human aerodigestive tracts from other mammals, including primates, is it appropriate to directly apply information gained in animal studies to humans? As stated by Laitman (1993), "during the course of human evolution, our aerodigestive region has had to undergo considerable modification away from the two-tube system that was likely in place in our earliest, more 'ape-like,' ancestors to the condition we have today. These changes would have … occurred contemporaneously with parallel changes in central and peripheral neural control" (Laitman & Reidenberg, 1993). Additionally, variance across species has been postulated to correlate with reorganisation of central representation, such as specialized orofacial behaviours in primates. Rilling (1998), using in-vivo MRI scans of 44 primates from 11 species, found increased cerebellar volume may be independent from overall brain size or body weight results, suggesting that neural representation in primates is not similarly organized (Marino, Rilling, Lin, & Ridgway, 2000; Rilling & Insel, 1998). The evolution of the unique human aerodigestive tract may have required reorganisation of higher-order brain areas involved in

programming complex sequenced motor output, such as pharyngeal sequencing when swallowing. With the laryngeal descent at around two years of age, humans may be reliant on a more distinct, well-timed and coordinated pattern of pharyngeal constriction than infants or other mammals. As discussed by Laitman (1993), humans "are the exception to the general mammalian plan … any anatomical abnormality or neurological miscue may thus exacerbate this already precarious condition and increase coordination errors in respiration and swallowing" (Laitman & Reidenberg, 1993).

The hypothesis that mis-sequencing is a result of neurologic impairment is supported by the finding of one brainstem stroke patient in the present study (n = 2) who demonstrated markedly reduced peak-to-peak separation in the first assessment session, recovering over time. However, if pharyngeal mis-sequencing was a result of brainstem damage, it is unclear why the PD cohort from the Ali et al. (1996) study, who show no discrete brainstem damage, reportedly demonstrate signs and symptoms consistent with pharyngeal mis-sequencing. Currently, it is unclear how the mis-sequencing seen in PD fits in with clinical findings and limited reports found in the literature. In the present study, none of the patients with PD (n = 3) present with pharyngeal mis-sequencing, e.g.,.within the 95% CI of the patient cohort reported by Huckabee et al. (2014). The ongoing prevalence study in patients with known neurological impairment may help to further understand the mechanism underlying this unique pathophysiologic presentation. Evaluation of a variety of dysphagic patient populations in the ongoing study will contribute greater insight into underlying aetiology by further delineating site of lesion in patients who present with mis-sequencing.

7.3 Pharyngeal mis-sequencing as a primary result of maladaptive compensation

The development of mis-sequencing as a maladaptive compensation in response to chronic dysphagia is another proposed explanation for this unique pathophysiologic presentation. All patients in the Huckabee et al. (2014) case series presented with chronic dysphagia, greater than 6 months post-onset, consistent with the Ali et al. (1996) study. Further reports of modification of pharyngeal pressure generation following rehabilitation is just one of many arguments in support of pharyngeal mis-sequencing as a spontaneous, maladaptive compensatory response to chronic dysphagia (Huckabee et al., 2014). In the case series (Huckabee et al., 2014), some patients being able to volitionally perform a mis-sequenced pattern by "swallowing hard." The effortful swallow, whereby patients are instructed to

'swallow hard,' was initially developed to compensate for reduced base of the tongue to the posterior pharyngeal wall contact and improve bolus transit (Logemann, 1998). In subsequent years, effortful swallowing has been included in routine clinical rehabilitation, despite conflicting reports of its effects on the biomechanics of healthy and impaired swallow function (Bülow et al., 1999, 2001, 2002; Garcia et al., 2004). In a study using manofluoroscopy, Bülow (1999) evaluated the effects of the supraglottic swallow, effortful swallow and chin tuck manoeuvre on swallowing biomechanics of healthy participants (n=8). When performing an effortful swallow, all participants demonstrated elevation of the hyoid bone prior to swallowing. During swallowing, the authors reported the effortful swallow significantly reduced hyoid excursion ($p = 0.01$), with subsequently significantly reduced laryngeal elevation during the swallow ($p = 0.01$). Due to the importance of hyolaryngeal excursion for epiglottic deflection, airway protection and UES opening, these findings raise concerns regarding the potential for effortful swallowing to worsen dysphagic signs (Bülow et al., 1999).

Garcia (2004) reported a case study of a 12-year old post exophytic brainstem glioma tumour resection with chronic dysphagia and reliance of percutaneous endoscopic gastrostomy (PEG) for nutrition. Eight months post-onset, the patient was instructed in effortful swallowing. Shortly thereafter, the patient began experiencing significant nasal redirection when swallowing, despite use of palatal lift with adequate velar movement when swallowing on VFSS. Due to nasal redirection on 100% of trials, the effortful swallow manoeuvre was untrained, with focus on teaching an effortless swallow. The authors report incidence of nasal redirection steadily declined, observed in less than 10% of trials following two weeks of effortless (rather than effortful) swallowing (Garcia et al., 2004). The authors caution that signs of dysphagia (e.g., nasal redirection) may not always represent physiologic abnormalities (e.g., reduced velopharyngeal closure) and potential maladaptive applications of compensations and rehabilitation should be considered (Garcia et al., 2004).

However, if pharyngeal mis-sequencing were a result of maladaptive compensation, it would present at later follow-up sessions, which was not reflected in the results presented in this thesis. It is clear that the pilot data collected as part of this thesis cannot resolve theses issues. However, the larger, ongoing study will provide critical information to help guide best practice for clinicians, patients with neurologic disorders and researchers of dysphagia. The

results will have direct benefits for improved health outcomes by aiding clinicians in their choice of instrumented evaluation and selection of management approaches. Current best practice in evaluation of dysphagia relies heavily on the use of VFSS to generate not only diagnoses but rehabilitation recommendations as well. However, when relying on a single tool in the evaluation of dysphagia, clinicians may be biasing their diagnosis and treatment. Future studies may provide the necessary information to encourage the use of more sensitive and appropriate diagnostic tools, such as inclusion of pharyngeal manometry or manofluoroscopy in comprehensive evaluations of dysphagia. This point is critical, as a misdiagnosed swallowing impairment cannot be treated effectively and may exacerbate impairment. Thus, the results of the ongoing research will not only translate immediately to improved patient care, but also provide greater scientific understanding of the complex neural control of swallowing. Further knowledge of aetiology and development of pharyngeal mis-sequencing will make management techniques more appropriate, safe and physiologically specific.

Chapter 8: Volitional Control of Pharyngeal Swallowing in Healthy Adults[8]

8.1 Introduction

The rhythmic pharyngeal phase of swallowing is controlled by a CPG through interconnections between the NTS and the NA in the medulla (Amri et al., 1984; Jean et al., 1975). This understanding is based on a series of animal studies, where patterned and replicable timing of the pharyngeal swallow has been evoked, even in decerebrate animals (Dick, Oku, Romaniuk, & Cherniack, 1993; Ertekin & Aydogdu, 2003; Jean, 2001; Miller, 2002). Historically, it has been accepted that few parameters of pharyngeal swallowing are amenable to volitional alteration. For example, Ertekin (2011) states "the regions of the cortex and subcortical areas involved with swallowing serve mainly to trigger deglutition and to control the beginning of the motor sequences (i.e., mainly the oral phase of swallowing). After this, sequential muscle activation is carried out without any further cortical control to perform the pharyngeal and esophageal phases" (p. 183). Over time, however, further understanding of modulatory cortical influence on the CPG driven pharyngeal swallow has suggested a greater capacity for pharyngeal change (Babaei et al., 2013; Hamdy et al., 1999, 2001; Huckabee et al., 2003; Martin et al., 2001).

Research using techniques such as fMRI have contributed evidence that a complex array of cortical structures, including the insular, primary motor and primary sensory cortices are activated during pharyngeal swallowing (Barritt & Smithard, 2009; Malandraki, Johnson, & Robbins, 2011). A complex relationship between cortical and bulbar structures may allow the capability to volitionally alter select parameters of swallowing, such as strength and duration, in response to peripheral afferent information (Ertekin, 2011; Malandraki et al., 2009). As concluded by Humbert & German (2013), "there are tantalizing data that suggest various facets of oropharyngeal motor control [interact] at various levels of the CNS during the normal swallow. However, the debate of whether the pharyngeal portion of the swallow is a reflex continues" (p. 8). This debate centres on whether the motor sequence of the pharyngeal swallow remains constant, even in the presence of cortical modulation (Ertekin & Aydogdu, 2003; Hamdy et al., 2000; Malandraki et al., 2011). For example, the effortful swallow,

[8] Some content from this chapter was published as Lamvik, K., Jones, R., Huckabee, M-L. (2015). The capacity for volitional control of pharyngeal swallowing in healthy adults. Physiology and Behavior, 1(152): 257-63.

whereby patients are instructed to ‘swallow hard’, has been shown to increase the overall amplitude of pharyngeal pressure (Bülow et al., 1999, 2001; Hind, Nicosia, Roecker, Carnes, & Robbins, 2001; Takasaki et al., 2011; Witte et al., 2008). Similarly, manoeuvres such as the Mendelsohn, aiming to increase duration of UES opening and volitional laryngeal vestibule closure, targeting increased duration of airway closure, have been shown to increase the overall duration of the pharyngeal swallow (Fukuoka et al., 2013; Hoffman et al., 2012; Macrae, Anderson, Taylor-Kamara, & Humbert, 2014; Wheeler-Hegland, Rosenbek, & Sapienza, 2008). From these studies, it is accepted that humans can volitionally modulate pressure and duration of contraction of the pharyngeal swallow, in its entirety (Peck et al., 2010). But, it is still unclear if humans are capable of modulating select components of the pharyngeal swallow in isolation, such as the temporal sequence of pharyngeal closure.

Importantly, recent studies have added evidence regarding cortical contribution to the temporal sequencing of swallowing. German et al. (2009) investigated the consistency of rhythmic muscle activation in decerebrate versus intact pig models using synchronized EMG and VFSS. They reported that most of the temporal pharyngeal sequence from the reflexive swallow seen in the decerebrate animal group was also observed in the intact animal group, but the sequence of specific activity, such as geniohyoid activation, was substantially altered in the intact animal group (German et al., 2009). It remained unclear if humans possess the capability to volitionally alter discrete sequential elements of the overall motor plan of the pharyngeal phase of swallowing and, if so, to what extent.

As described in Chapter 7, Huckabee et al. (2014) used pharyngeal manometry as a visual biofeedback modality in an intensive rehabilitation paradigm for a cohort of patients presenting with pharyngeal mis-sequencing. At the initiation of rehabilitation, once educated on the visual output generated from pharyngeal manometry, patients were instructed to volitionally increase the temporal separation between the proximal and distal pharyngeal pressure waveforms when swallowing. Following daily treatment, the mean latency between peak pressures at the proximal and distal pharynx increased from a pre-treatment average of 15 ms to a post-treatment mean of 137 ms (95% CI = 86–187 ms). It was conjectured that these patients were able to volitionally generate a cortical pharyngeal motor plan that either replaced or substantially modulated the medullary CPG motor plan, increasing temporal latency of proximal to distal pharyngeal closure when swallowing. The presence of such a

capability was suggested by German et al. (2009). This aligns with patient reports of the need to maintain conscious awareness of swallowing to ensure generalization of gains following rehabilitation. However, this independent alteration in the latency of pharyngeal closure, as a representation of altered sequential muscle activation, challenges the commonly-held belief that the pharyngeal phase of swallowing is an involuntary reflexive sequence (Ertekin & Aydogdu, 2003; Miller, 2002).

The aim of this exploratory study was to evaluate the capacity of healthy humans to volitionally alter the 'reflexive' components of the pharyngeal swallow. The investigators sought to determine if healthy participants, upon completion of an intensive training protocol, could learn to modulate the temporal characteristics of peak pharyngeal pressure, specifically the latency of pressure generation between the proximal and distal pharynx using pharyngeal manometry as visual biofeedback. In essence, the investigators evaluated the participants capacity to replicate the initial presentation of the patient cohort with pharyngeal mis-sequencing (Huckabee et al., 2014). It was hypothesized that normal healthy adults would be able to adopt a motor plan which recruited pharyngeal pressure in both the proximal and distal pharynx, with a substantially reduced peak-to-peak separation between pharyngeal manometric sensors, following two weeks of daily biofeedback training. This would be accomplished without a simultaneous reduction in total swallowing duration, suggesting that the adaptation was one of volitional temporal shift of a specific component of swallowing rather than a more synergistic reduction in overall swallowing duration. This point is critical, as a proportionate reduction in swallowing duration would imply participants are merely swallowing at a faster rate, rather than altering the motor plan by disproportionately altering latency of pharyngeal closure in isolation. Successful modulation of the sequence of pharyngeal pressure generation by cortical control mechanisms would provide evidence to challenge the assumption that the sequence of pharyngeal pressure generation is a fixed and patterned reflexive response, unable to be cortically modulated. This would likely have important implications in the design of new approaches to dysphagia rehabilitation.

8.2 Materials and Methods

8.2.1 Participants

Six healthy participants (3 males, 3 females), ranging in age from 19 to 44 years (mean = 29 years), participated in the study. No participant reported a history of dysphagia, neurological

or muscular impairment, or use of any medications that might have affected swallowing. Ethical approval was obtained from the local institutional review board and informed consent was obtained from all participants prior to commencement of data collection.

8.2.2 Equipment

A 100-cm long catheter, 2.1 mm in diameter (Model CTS3 + EMG, Gaeltec, Hackensack, NJ, USA), was used for manometric data collection. As per standardized catheter recommendations from Salassa, DeVault, & McConnel (1998), the catheter housed 3 solid-state, unidirectional, posteriorly-oriented sensors (2 x 5 mm) with 2 cm spacing between sensors 1 and 2, and 3 cm between sensors 2 and 3. Pressures were measured at the proximal pharynx, distal pharynx and UES with sensors 1, 2 and 3 respectively. The catheter was connected to the Kay Elemetrics Digital Swallowing Workstation (Model 7120, Kay Pentax, Lincoln Park, NJ, USA), with digitized recording of pressure waveforms as a function of time displayed in real time in a -100 to 500 mmHg display window on a computer screen and digitally recorded for offline analysis.

8.2.3 Procedures

All participants were seen for intensive, skill-based training five days per week for a period of two weeks (10 days), for a total of 10 one-hour sessions. This intensity was chosen to reflect the duration of intensive patient treatment used in local rehabilitation protocols (Huckabee et al., 2014). Participants were seated upright in a comfortable chair. During each session, pharyngeal manometry was used as a visual biofeedback modality. At the beginning of the session, participants were shown images of manometric waveforms depicting normal pharyngeal pressure during swallowing, as shown in Figure 8.1. Participants were educated on the goal of the training session, namely to reduce the separation between the peaks of the upper and lower pharyngeal sensors.

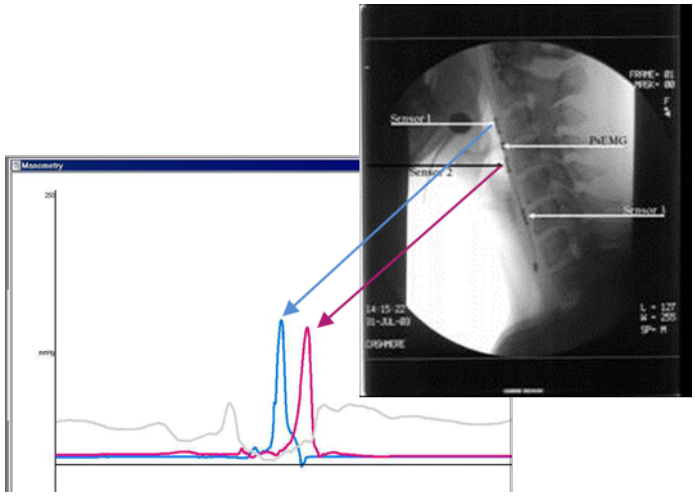


Figure 8.1 Sample manometric waveforms used for participant training. The blue line indicates pressure generation in the proximal pharynx while the red line indicates pressure generation in the distal pharynx. (See Huckabee et al., 2014; p. 156).

The lubricated intraluminal catheter was inserted into one naris, using routine clinical and research protocols (Huckabee et al., 2014). A pull-through technique was performed in 5-mm increments. This was continued until correct catheter placement was confirmed through visualization of the typical 'M' wave at sensor 3 during swallowing, corresponding to the superior aspect of the high pressure zone of the UES (Castell & Castell, 1993). Posterior orientation of the three sensors was confirmed by monitoring unidirectional markers on the catheter. The catheter was then secured to the nose with medical tape. At final placement, sensor 1 was located in the proximal pharynx (approximately at the level of the base of tongue), sensor 2 in the distal pharynx (approximately at the level of the laryngeal additus) and sensor 3 in the proximal aspect of the UES. Throughout data collection, evaluation of manometric waveforms by the researcher ensured correct placement was maintained. As modulation of UES function was not a focus of training, once placement was ensured, the waveform of sensor 3 was desaturated in colour to reduce visibility and to increase participant attention to the waveforms of sensors 1 and 2.

Each session consisted of collection of pre-training baseline swallows, to monitor whether training alters each participant's underlying swallowing motor plan, followed by three 15 min blocks of training utilizingthe visual biofeedback and ending with post-training swallows without visual biofeedback. To record baseline data, the computer monitor was turned away

from the participants and they were asked to produce five typical (i.e., "normal") saliva swallows, without visualization of the waveform. Following the acquisition of baseline data, the participants were positioned to face the computer monitor. Using the real-time manometric data on the screen as visual biofeedback, the participants attempted to adapt swallowing behaviour to produce simultaneous pressure in sensors 1 and 2, performing dry swallows at a self-generated pace, approximately every 30–45 s. Directions included "try to make the red line come before the blue line" or "try to make your waveforms overlap." Sips of water were offered as needed to moisten the mouth. When the participants completed the three 15 min blocks of training, they were asked to perform their five 'best' mis-sequenced swallows without biofeedback (e.g., the computer monitor was turned away from the participants). Following these five swallows, the catheter was removed from the nasopharynx and the session ended.

8.2.4 Data analysis

Five baseline swallows, a randomly-selected 20% of swallows within each training session and five post-training swallows without visual biofeedback were measured off-line for each subject using Kay Digital Swallowing Workstation software. Temporal values were measured with manually-placed, digital cursors for peak latencies of pharyngeal pressures generated at sensors 1 and 2 with peak-to-peak latency calculated as the difference between these two cursors. Total swallowing duration was measured from onset of pressure at sensor 1 to the offset of pressure at sensor 2. As measurement of onset measures were found to have poorer inter-rater reliability, swallowing onset and offset were measured at the point where the waveform crossed a horizontal cursor placed at 10% above the resting baseline, to remove bias in determine the onset of the waveforms. Amplitude data were measured using automated detection software to identify peak amplitude and subsequently compared to peak-to-peak latency. Data were analysed using SPSS statistical software (IBM SPSS Statistics for Windows, Version 21.0, 2012, Armonk, NY: IBM Corp.).

Non-parametric statistics were used due to the small sample size in the study and non-gaussian distribution of the data (Shapiro-Wilk test, $p < 0.01$). Statistical analyses included descriptive statistics reporting medians and IQR for all measures at baseline, session 5 and session 10. Friedman's tests, similar to the parametric repeated-measures analysis of variance, were used to detect differences in latency and total swallowing duration across

participants for baseline, session 5 and session 10. Post-hoc pair-wise comparisons were completed with a Wilcoxon signed-rank test. Pearsons product-moment correlation coefficients were used to analyse the relationship between change in peak-to-peak latency to change in average peak amplitude (across sensor 1 and 2) and swallowing duration, respectively. Inter- and intra-rater reliability (using a random 20% subset of the extracted randomized data) was analysed using two-way mixed ICC. The rater was a speech-language pathologist familiar with analysis of manometric waveforms, but naïve to the study aim and outcomes. The rater was provided the above definitions of latency and duration measurements. As amplitude data were collected with automated detection software, reliability analysis was not undertaken for this measure. The rater was blinded to sessions and participants and sessions were randomized during the reliability data collection procedure.

8.3 Results

All participants completed the intensive training protocol without any adverse events. Intra-rater reliability was high across measures (ICC = 0.97). Inter-rater reliability between two trained speech-language pathologists showed an excellent level of concordance for measures of peak-to-peak latency (ICC = 0.98) and total swallowing duration (ICC = 0.92).

8.3.1 Baseline Swallowing

Baseline swallows collected at the beginning of each training session were consistent over the training period, with no significant differences between baseline measures at sessions 1, 5 and 10 for peak-to-peak latency (p = 0.12) and total swallowing duration (p = 0.31). Table 1 depicts baseline swallows across all training sessions.

Table 8.1 Median (IQR) baseline swallowing, as averaged between all sessions.

Measure	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	Participant 6
Peak-to-peak latency	60 ms (56 ms)	84 ms (66 ms)	208 ms (79 ms)	103 ms (122 ms)	119 ms (154 ms)	239 ms (77 ms)
Swallowing duration	592 ms (70 ms)	610 ms (106 ms)	576 ms (194 ms)	555 ms (71 ms)	521 ms (120 ms)	700 ms (127 ms)
Onset duration	134 ms (48 ms)	76 ms (46 ms)	201 ms (56 ms)	102 ms (121 ms)	131 ms (58 ms)	305 ms (85 ms)

8.3.2 Training Sessions with Biofeedback

Based on Friedman's test analyses, there was a reduction in peak-to-peak latency ($p < 0.01$), but no significant changes in overall total swallowing duration ($p = 0.41$) between training performance from session 1 baseline to session 5 training and session 10 training. Session 1 pre-training and final session median and interquartile ranges are summarized in Table 2.

Table 8.2 Measures of pharyngeal swallowing (median and IQR) at session 1 pre-training and session 10 training.

Measure	Baseline	Session 5	% Change from Baseline	Session 10	% Change from Baseline
Peak-to-peak latency	188 ms (231 ms)	54 ms (97 ms)	71.3%	68 ms (92 ms)	63.8%
Swallowing duration	671 ms (254 ms)	623 ms (256 ms)	7.2%	595 ms (239 ms)	11.3%

Pairwise analyses with Wilcoxon signed-rank tests revealed differences between peak-to-peak latencies at session 1 baseline and session 1 training ($p = 0.05$), session 1 baseline and session 5 training ($p = 0.028$), session 1 baseline and session 10 training ($p = 0.03$). There was a difference between session 1 training and session 5 training ($p = 0.03$), but no significant change between training sessions 5 and 10 ($p = 0.60$), as shown in Figure 8.2. No significant differences were seen for total swallowing duration or amplitude between session 1 baseline and sessions 1, 5, or 10 training.

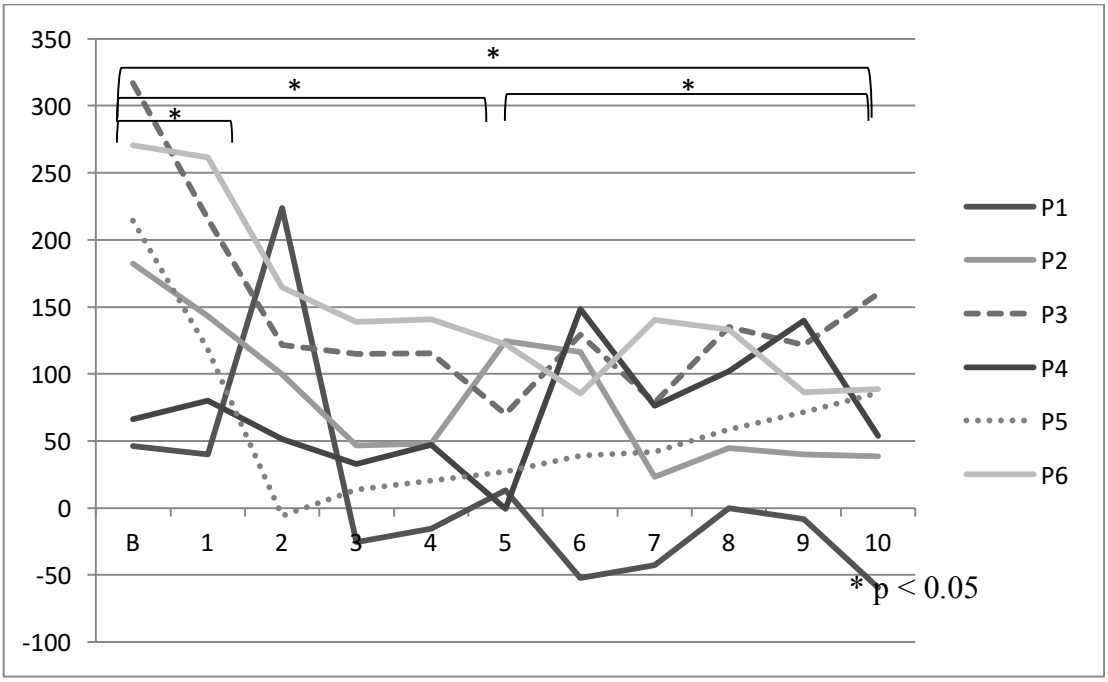


Figure 8.2 Median peak-to-peak latencies for each participant.

8.3.3 Post-Training without Biofeedback

Using a Friedman's test, results of the five post-training swallows at the end of each session, where participants were asked to volitionally modulate their swallow without biofeedback, were compared from session 1 baseline with post-training at sessions 1, 5 and 10, respectively. Participants demonstrated a reduction in peak-to-peak latency from a pre-training baseline median of 188 ms (IQR = 231) to 67 ms (IQR = 87; $p = 0.03$) at the end of session 10. In contrast to the findings from the training swallows, there was a difference between post-training swallows for total swallowing duration ($p = 0.03$), from an initial baseline median of 670 ms (IQR = 254) to a post-training median of 545 ms (IQR = 197). Pairwise analysis with Wilcoxon signed-rank test was also investigated between pre-training baselines versus post-training swallows without biofeedback at sessions 1, 5 and 10 (Table 8.3).

Table 8.3 Comparison of post-training swallows, without biofeedback, to initial baseline swallows.

	Peak-to-Peak Latency Median (IQR)	**Comparison to Baseline (*p < 0.05)**	**Swallowing Duration Median (IQR)**	**Comparison to Baseline (*p < 0.05)**
Session 1 Baseline	188 ms (231)	-	670 ms (254)	-
Session 1 Post-Training	132 ms (156)	0.17	506 ms (835)	0.03*
Session 5 Post-Training	30 ms (105)	0.03*	650 ms (311)	0.60
Session 10 Post-Training	67 ms (87)	0.03*	545 ms (197)	0.12

Comparisons with a Wilcoxon signed-rank test were used to determine the relationship between peak-to-peak latency of training swallows with biofeedback to post-training swallows without biofeedback in each session. There were no significant differences between latency from training with biofeedback to post-training without biofeedback within that same session. This confirms a consistent level of volitional control of modulation with biofeedback and immediately after suspending visual biofeedback within sessions.

8.3.4 Correlation between Swallowing Features

Pearsons product-moment correlation coefficient was used to analyse the relationship between change in peak-to-peak latency to change in average peak amplitude during training to determine if there was a relationship between reduced latency of pharyngeal closure with increased amplitude of pharyngeal swallowing, as participants reported increased ease in altering timing of pharyngeal closure when swallowing hard. Determinant of change was calculated by subtracting median values from baseline to training sessions 1, 5 and 10, respectively, within each subject for all participants. There was a linear correlation between peak amplitude and peak-to-peak latency ($r = 0.57$), as depicted in Figure 8.3.

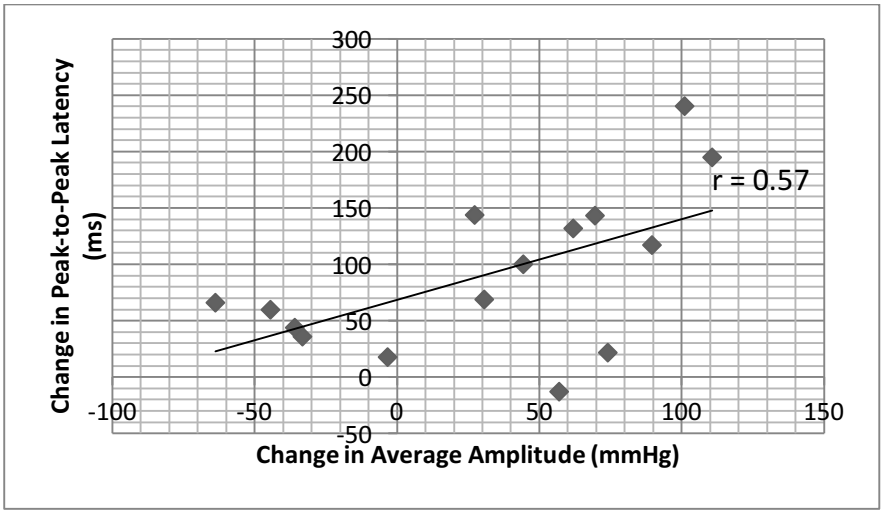


Figure 8.3 Relationship between change in average amplitude and peak-to-peak latency during training (with biofeedback).

A similar analysis with Pearsons product-moment correlation coefficient was used to analyse the relationship between change in peak-to-peak latency and change in total swallowing duration during training to determine if there was a relationship between reduced latency of pharyngeal closure with a proportionate reduction in total swallowing duration. Determinant of change was calculated by subtracting median values from baseline to sessions 1, 5 and 10, respectively, within each subject for all participants, as used above. There was a linear correlation between peak amplitude and peak-to-peak latency (r = 0.444), as depicted in Figure 8.4.

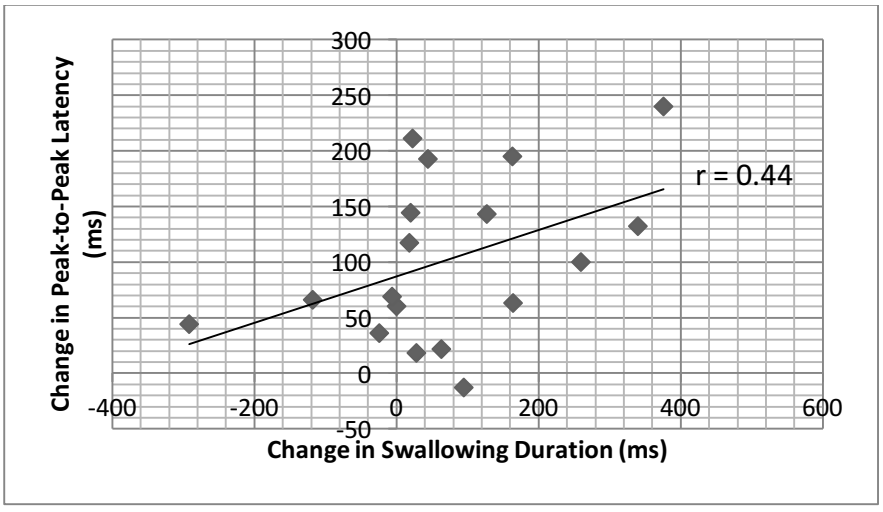


Figure 8.4 Relationship between change in total swallowing duration and peak-to-peak latency during training (with biofeedback).

8.4 Discussion

This exploratory study is the first to have evaluated the capacity of healthy adults to modulate the latency of pressure generation between the proximal and distal pharynx. Given intensive manometric biofeedback training, participants were able to substantially reduce the temporal separation between the peaks of the pharyngeal waveforms when volitionally swallowing and maintain this gain immediately following the session without biofeedback. However, there was no further reduction seen during the second week of training. This indicates an effective limit in the newly acquired skill of volitionally altering pharyngeal sequence. Further, the median peak-to-peak latency achieved by the healthy participants (68 ms) was still above the 95% confidence interval of peak-to-peak latencies reported in the mis-sequencing patient group (15 ms, 95% CI, -2 to 33 ms; Huckabee et al., 2014). The limit in gains suggests that volitional modulation cannot alter the reflexive pharyngeal sequence to a pathologic level, as observed in the patient cohort.

The observation that participants had no significant change of pharyngeal timing in baseline 'normal' swallowing across the two-week training period suggests that there was limited neural change, either at a cortical motor-planning level overriding the brainstem response, or at the brainstem level of the medullary-mediated pharyngeal swallowing sequence; however, this was not evaluated explicitly. Conversely, once biofeedback was provided after the baseline swallows, participants were able to volitionally alter swallowing peak latency, albeit not without considerable 'intra-session experimentation' in modulating the parameter of interest. Assessment with pre- and post-training fMRI could provide insights into neural change associated with this adapted pharyngeal response.

As described in Chapter 7, Huckabee et al. (2014) speculated on the aetiology of the pathophysiologic feature of mis-sequencing and questioned whether this was a maladaptive response to impairment or reflected a feature of impairment from the brain injury itself. The healthy cohort in the present study provides evidence regarding the capability to alter the pharyngeal sequence with voluntary control. Interestingly, both the patient cohort described by Huckabee et al. (2014) and healthy participants in the current study reported increased ease producing a mis-sequenced pattern when swallowing with effort. This finding is supported by a moderately strong relationship between change in peak-to-peak latency and change in peak amplitude ($r = 0.57$). Additionally, both cohorts similarly reported the need to

maintain conscious attention during the biofeedback task to implement the desired pharyngeal response. As seen in the subgroup of patients reported by Huckabee et al (2014) who did not benefit from treatment, three of the six subjects in the current study regressed by session 10, with peak-to-peak latency increasing from gains made at session 5. It is unclear if this regression reflects a loss of skill, variance due to small sample size or loss of attention and motivation during participation.

An important distinction needs to be made with regard to the proportion of change of latency of pharyngeal closure to total swallowing duration. Although participants were able to substantially reduce their peak-to-peak separation between pharyngeal manometric sensors without a simultaneous significant reduction in total swallowing duration during training swallows, there was a significant reduction in swallowing duration during the post-training swallows without biofeedback. This, in conjunction with the finding of a moderate relationship between change in peak-to-peak latency and change in swallowing duration ($r = 0.44$), indicates that participants are in large part merely modulating total swallowing duration to achieve the goal, rather than altering latency of pharyngeal closure in isolation. Although it is accepted humans can volitionally modulate amplitude and duration of contraction of the pharyngeal swallow, in its entirety, it is still unclear if humans are capable of modulating the select components of the pharyngeal swallow in isolation, such as timing of pharyngeal closure. Further research is needed to clarify this point with discrete elements of pharyngeal swallowing. This specificity is critical to understand the capability of fundamentally altering the pharyngeal motor plan, rather than optimizing the current plan (e.g., swallowing faster).

Biofeedback likely played a critical role in the ability to maximize cortical capacity to modulate aspects of pharyngeal swallowing, a reflexive function which is otherwise difficult to envisage. Other studies have evaluated the effect of biofeedback-enabled volitional modulation of presumed reflexive parameters of swallowing, such as UES opening and airway protection. Kahrilas, Logemann, Krugler, & Flanagan (1991) used tactile biofeedback in conjunction with swallowing manoeuvres change to alter in UES opening in healthy participants (n=7), as evaluated by manofluoroscopy. Similarly, Macrae et al. (2014) trained healthy participants (n=16) to perform a volitional laryngeal vestibule closure manoeuvre during swallowing either with or without biofeedback. Results indicated participants in the

biofeedback group made significant improvement in duration of laryngeal vestibule closure, while there were no difference from baseline in the no feedback group (Macrae et al., 2014). Although these studies indicate that UES opening, hyoid movement and laryngeal vestibule closure are amenable to alteration by volitional control, the basic sequence of pharyngeal swallowing was not altered. From studies of pig models, German et al. (2009) concluded that humans may have only certain muscle groups or components of pharyngeal swallowing capable of cortical modulation and, even then, only to a certain degree. This may have important implications when considering rehabilitation design and implementation. Understanding a healthy individual's capability to volitionally alter select components of pharyngeal swallowing is vital, as humans can utilize this capability for cortical control during behavioural rehabilitation of impaired swallowing physiology (Humbert & German, 2013). However, it is critical to understand the impact that targeted rehabilitation has on the pharyngeal swallowing response overall. As the pharyngeal swallow is a highly orchestrated response, isolating targeted aspects can have unintended effects on the gestalt, as reported, for example, with increased nasal redirection as a result of an effortful swallowing paradigm (Garcia et al., 2004).

Our study has limitations, which are important to acknowledge. The study was limited by small sample size, compounded by the use of non-parametric statistics, which may under-power findings and place the study at risk for Type II error. Additionally, pharyngeal manometry does not directly allow visualization of swallowing physiology. Further research is indicated using manofluoroscopy to enable visual assessment of changes of biomechanics pre- and post-training to quantify how a change in pharyngeal timing affects swallowing parameters, if at all. Incorporation of videofluoroscopic evaluation can also provide insight on possible alteration of associated parameters during modulation of pharyngeal swallowing, such as pharyngeal shortening and coordination with UES and laryngeal functioning. Further, as the manometric catheter was placed intraluminally, it is unknown whether the participants utilized any tactile feedback during the training task. Additionally, as pressure is a proxy measure for timing of muscle contraction, a study utilizingpharyngeal EMG would be of value for further analysis of specific changes in temporal activation of muscle contraction itself. As this study did not include follow-up assessments after the two-week training period, ongoing data collection would be beneficial to determine the extent to which this new

volitional control over pharyngeal swallowing is retained, without further biofeedback training or practice in healthy subjects.

Chapter 9: Pharyngeal Swallowing during Wake and Sleep States[9]

9.1 Introduction

As discussed throughout this text, an over-arching goal of this thesis is to evaluate differences in volitional versus reflexive pharyngeal swallowing. While the previous chapter investigated swallowing under maximal volitional control, questions remain regarding biomechanical characteristics of truly reflexive swallowing in humans. Research has utilized techniques such as measurement of spontaneous wake swallows (Ertekin et al., 2013) or provision of bolus material directly into the pharynx to evaluate reflexive swallowing (Al-Toubi et al., 2015). Yet, it remains unclear if spontaneous swallows are influenced by persistent conscious or subconscious cortical input that modulate swallowing and if they are truly representative of the swallowing reflex (Kelly, Huckabee, & Cooke, 2006). Thus, evaluating swallowing during sleep may serve an important role in the assessment and understanding of the reflexive pharyngeal swallowing response.

Sleep has been associated with periods of relative cortical quiescence as a result of active input from structures such as the pontine reticular system (Hobson & Pace-Schott, 2002; Orr et al., 2004). Beginning the transition from wake to sleep, non-rapid eye movement (NREM) sleep enables slowing of autonomic processes, with reductions in heart rate, blood pressure and metabolism. However, unlike NREM, rapid eye movement (REM) sleep consists of paralyses of skeletal muscles with suspension of regulatory mechanisms responsible for body temperature, pH, regulation of blood oxygen, among other processes, with heightened cortical processing similar to wake states (Orr et al., 2004). Initial REM sleep lasts approximately 90 min, increasing in duration as the night progresses (Orr et al., 2004). Muscle relaxation during sleep co-occurs with strong suppression of sensory reception (Inoue, Yamamura, Nakajima, & Yamada, 1999). This is demonstrated by Issa et al. (1994) who infused gustatory stimuli to the anterior and posterior tongue surface in attempts to elicit swallowing in dogs (n = 4). Robust swallowing triggered when awake contrasts to sleep states in which the gustatory stimuli was unable to trigger a swallow or elicit arousal followed by swallowing in the same animals (Issa, 1994). Although the authors concluded that wakefulness is a prerequisite for swallowing, numerous studies have documented

[9] Esther Guiu Hernandez contributed substantially to data analysis in this chapter.

swallowing during sleep in humans (Ertekin, 2011; Lichter & Muir, 1975; Pohl et al., 2013; Sato & Nakashima, 2006).

The earliest investigation of swallowing during sleep arose due to concerns regarding nocturnal gastroesophageal reflux, over forty years ago. In a study of healthy individuals (n = 10), Lichter & Muir (1975) evaluated swallowing during sleep, using polysomnography to monitor sleep staging (comprised of cephalography (EEG), electrooculography and body movement sensors). The authors adapted a foetal heart monitor, attached to the external laryngeal region, to monitor laryngeal movements and sounds of swallowing. Results indicated that swallowing was episodic with long periods absent of swallowing (Lichter & Muir, 1975). Subsequent to this study, the majority of investigation of sleep-related deglutition focus on evaluation of the oesophagus in combination with pH testing (Orr et al., 2004, 1984; Pasricha, 2003; Pohl et al., 2013), sleep swallowing in pre-term infants (Jadcherla, Chan, Fernandez, & Splaingard, 2013; Jeffery, Ius, & Page, 2000) and investigation of sleep apnoea (da Paz Oliveira, de Souza Fontes & Cahali, 2015; Don & Waters, 2003; Reda, Gibson, & Wilson, 2001; Teramoto et al., 1999; Teramoto, Ishii, & Matsuse, 2001; Tvinnereim, Cole, Haight & Hoffstein, 1995). Currently, it is accepted there is a marked reduction in oropharyngeal swallowing frequency, coupled with a decrease in UES pressure and increase or no change from wake states in LES pressure during sleep (Eastwood, Katagiri, Shepherd, & Hillman, 2007). This occurs in conjunction with a dramatic reduction in saliva production during sleep (Schneyer et al., 1956). Taken together, this illustrates the increased nocturnal role of the oropharynx for respiration and the susceptibility to increased episodes of gastroesophageal reflux (Kahrilas, 1994).

However, evaluation of oropharyngeal swallowing during sleep has centred around denotation of frequency of swallowing, rather than quantification of specific biomechanics (Sato & Nakashima, 2006, 2007; Sato, Umeno, Chitose, & Nakashima, 2011). For example, Reda et al. (2001) evaluated healthy subjects with low-resolution pharyngeal manometry during polysomnography, however, the aim was investigating feasibility of manometry in evaluating sleep apnoea and differences in amplitude or timing of swallowing during sleep were not reported (Reda et al., 2001). More recently, Sato et al. evaluated swallowing during sleep across the lifespan in three separate studies with polysomnography and simultaneous sEMG of suprahyoid and thyrohyoid muscles (Sato & Nakashima, 2006, 2007; Sato et al.,

2011). They reported frequency of swallowing per hour, namely 2.9 (SD = 1.3) swallows per hour during sleep in healthy adults, with the greatest number of swallows per hour during transition from wake to sleep (stage 1; 7.2, SD = 3.5) and the least during later-stage NREM sleep (stage 4; 0 swallows per hour). While this provides important data regarding the reduced frequency of swallowing during sleep as compared to 24.4 (SD = 8.7) swallows per hour when awake (Lear, Flanagan, & Moorrees), further research is needed to characterize differences in swallowing biomechanics during wake and sleep states.

To this end, studies have evaluated timing of swallowing onset during sleep in response to bolus material. Pinto et al. (1994) evaluated swallowing during sleep with healthy participants (n = 10) and patients with either cerebral atrophy or lacunar infarct (n = 25). An intraluminal catheter was placed transnasally to deliver 1 mL water to the pharynx. Swallowing was measured by sEMG on the submental musculature. No difference was identified in response time to bolus presentation in controls between wake and sleep states, but 54% of the patients with neurologic impairment demonstrated >5 s delay in swallowing response when asleep as compared to when awake. While the authors concluded altered function of swallowing during sleep may place patients at greater risk of aspiration pneumonia, they did not theorize about possible mechanisms underlying the difference in onset of sleep versus wake swallowing (Pinto, Yanai, Nakagawa, Sekizawa, & Sasaki, 1994). This study was replicated with adult cats (n = 4) with implanted EEG and EMG electrodes (Anderson, Dick, & Orem, 1995). Swallowing was measured with submental EMG and intraluminal pharyngeal pressure, combined with an elastomer tube that provided three volumes of water (0.5 mL, 0.19 mL, 0.06 mL). While the authors concluded that swallows during wake and NREM conditions are comparable, they also found that larger volumes of fluid produced a higher number of swallows in NREM sleep than when awake. These studies provide early evidence to support the possibility of differences in sleep swallowing beyond frequency of swallowing, with the potential for reduced accuracy in the accommodation of boluses of varying sizes due to reduced transmission of afferent sensory feedback during sleep. Similarly, swallowing-respiratory coordination has been shown to be affected by the degree of volitional input, with increased variability in coordination of breathing and swallowing during sleep (Kelly et al., 2006, 2007).

Despite these publications, little is known about differences in timing and amplitude of pharyngeal pressure during swallowing in sleep and wake states. Even less is known about swallowing during sleep in patients with dysphagia. Thus, the present study evaluated the pharyngeal swallowing response during sleep. This may inform on the role of volition and arousal in control of pharyngeal swallowing. It was hypothesized that healthy and impaired participants would demonstrate a significant difference between baseline and sleep swallowing parameters, with shorter total pharyngeal duration and lower amplitude when asleep. Differences in pharyngeal pressure measures between sleep and wake states would suggest a significant role of cortical modulation of the pharyngeal swallowing response that may inform the development of rehabilitation protocols.

9.2 Materials and Methods

9.2.1 Participants

Twenty-two healthy participants (4 males, 18 females), ranging in age from 21–52 years (mean = 27 years) were recruited for this study. No participant reported a history of dysphagia, neurological or muscular impairment, or use of any medications that are known to affect swallowing or sleep. Three patients with dysphagia characterized by pharyngeal mis-sequencing were also recruited, with diagnoses reported in table 9.1. These patients were chosen specifically to further investigate pharyngeal mis-sequencing during sleep. Ethical approval was obtained from the local institutional review board and informed consent was obtained from all participants prior to commencement of data collection.

Table 9.1 Summary of patient characteristics and diagnoses.

	Age	Gender	Diagnosis	Current Diet
Patient 1	48 yr	F	2 years post-resection of a tumour of the fourth ventricular epidermoid in the cerebellum	PEG
Patient 2	46 yr	M	7 years post-resection of clival meningioma	Normal diet, Thin liquids
Patient 3	33 yr	M	6 months post- multiple brain infarcts secondary to polycythemia rubravera	Soft diet, Thin liquids

9.2.2 Equipment

Healthy participants were evaluated with HRM, using the ManoScan 360™ High-resolution Manometry system (Model A120) with a 2.75-mm diameter ManoScan™ ESO catheter (EPS0042). In-vivo calibrations were routinely performed and each recording session was preceded by calibration per standard operating instructions. Patients were evaluated with low-resolution manometry, using a 3-sensor solid-state catheter (posteriorly-oriented sensors; ModelCTS3 + EMG, Gaeltec, NJ, USA), as discussed in Chapters 7 and 8. Patients were evaluated with low-resolution manometry in order to compare results with their prior clinical manometric examinations and rehabilitation training with low-resolution manometry. To date, it is not known how low- and high-resolution manometry differ in evaluation of pharyngeal swallowing, as discussed further in Chapter 11.

9.2.3 Procedures

Both HRM and low-resolution manometric catheters were placed transnasally using a routine protocol (Knigge et al., 2013; Lamvik et al., 2015). The protocol for low-resolution manometry is detailed in Chapter 7 (section 7.2.3) and 8 (section 8.2.3). This protocol is similar for HRM, with the exception of final catheter positioning. As HRM catheters contain 36 pressure sensors spaced 0.75 mm apart, a pull-through technique to enable optimal placement was not required. Thus, the HRM catheter was inserted until sensor 1 was located just inside the naris and sensor 36 in the cervical oesophagus, enabling the length of the upper aerodigestive tract to be evaluated in its entirety.

Once the low- or high-resolution catheter was inserted, it was taped securely to the external nose with medical adhesive tape and the participant was provided with a few minutes to accommodate to the presence of the catheter. Each subject was asked to perform five dry swallows at a self-generated pace, approximately one swallow every minute to record baseline function. Sips of water were offered as needed to moisten the mouth throughout. The participant was then assisted to achieve a comfortable supine position in bed. Following repositioning, subjects performed five dry supine swallows at a self-generated pace, approximately one swallow every minute with sips of water available as needed. Subsequent to this, participants were left alone to fall asleep with the catheter in situ. The researchers monitored the participant through observation of live manometric recordings throughout the night, displayed on an external computer monitor. The study was terminated when the

participant awoke the following morning, or at 8 hr following commencement of the sleep study.

9.2.4 Data Analysis

Data Correction

Pharyngeal pressure data from HRM were exported and analysed post-hoc with external software (MATLAB R2014a, The MathWorks Inc., Natick, MA, 2014). A notable measurement error was identified in the manometric recordings (Figure 9.1), discussed at length in Chapter 13. The investigators were unable to correct this drift using the compensation methods available on the ManoScan^{TM} software due to the study duration, as the standard TC method is only appropriate for short (<30 min) studies (Robertson et al., 2012). Therefore, a custom compensation was implemented in MATLAB. A best-fit line was generated from raw pressure data from each sensor across each study, as shown in Figure 9.1. As swallowing was infrequent during sleep, a linear regression enabled determination of baseline pressure throughout the recording, apart from outlier pressure above baseline (e.g., swallows). From this best fit line, outliers were identified and removed to generate a second best fit line, altered subtly in slope. The final best-fit line equation was compared to zero and any difference from zero was subtracted from each value of raw HRM data at each time point. This levelled the baseline and manually corrected the measurement error. This drift was not seen on low-resolution manometry.

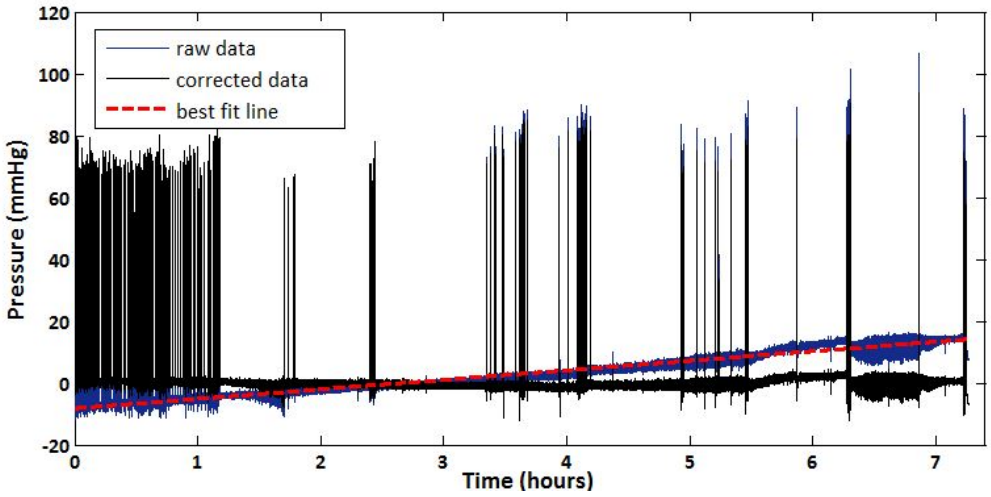


Figure 9.1 An example recording from a sample sensor revealed an altered pressure at the onset of the study and an increasing measurement error over time, with deviations greater

than 30 mmHg in some sensors. Raw data is plotted in blue, with the best-fit line represented in red. Raw data was corrected by re-aligning the pressure to a zero baseline, as shown in black.

Once measurement error was corrected, the latency and amplitude of pharyngeal pressure were measured. Individual swallows were annotated according to their condition, namely upright awake, supine awake and sleep. All measurements of sleep swallow were taken an hour after commencement of the sleep study. Three sleep swallow subtypes were identified in analysis of the raw data. These subtypes consisted of type 1, characterized by one swallow occurring without any activity in a surrounding 5 min period, type 2 characterized by a burst of three or more swallows occurring within a 5 min period and type 3 which included all other nocturnal swallows. As HRM and low-resolution manometry output is quite different, specific data analysis procedures will be described individually below.

High-resolution Manometry

Sensors in the pharyngeal region were extracted from the total 36 sensors by identifying the sensors immediately below the velopharyngeal regions (Knigge et al., 2014) and immediately above the most superior 'M-wave' channel representative of the UES region. Swallows were aligned temporally by annotating the onset of the uppermost pharyngeal sensor. Following this, swallows were averaged for each participant across the upright awake, supine awake and sleep conditions and the mean maximum pharyngeal pressure were measured. Three measures were utilized to investigate temporal characteristics of pharyngeal swallowing as HRM differs in measurement than low-resolution manometry. First, the duration of the pharyngeal phase was measured by evaluating the temporal latency between the maximum pressure in the upper pharynx to that in the lower pharynx, similar to measuring peak-to-peak latency in low-resolution manometry, as discussed below. Second, slope was measured for each participant by creating a best fit line of the average maximum for each pharyngeal sensor across the swallowing conditions. The slope allows measurement across a greater number of sensors, reducing the potential for poor inter-rater reliability inherent in individual sensor selection in measurement of HRM, as discussed in Chapter 12. Lastly, the position at first maximum pressure was evaluated to investigate differences in onset of pharyngeal swallowing across conditions. Parametric statistics were used as assumption of normality was satisfied for all group combinations as assessed by Shapiro-Wilk's test ($p > .05$). Comparisons

were made between upright and supine wake conditions as well as between supine wake and supine sleep conditions with paired-samples t-tests. Comparisons between the three sleep subtypes were made with a one-way ANOVA with post hoc comparisons (Tukey HSD). This was completed with SPSS statistical software.

Low-resolution Manometry

All swallows were measured off-line for each subject using Kay Digital Swallowing Workstation software. As swallows could be measured without need for external correction of measurement error, data analysis was increasingly straightforward with low-resolution manometry. Temporal values were measured with manually-placed, digital cursors for peak latencies of pharyngeal pressures generated at sensors 1 and 2 with peak-to-peak latency calculated as the difference between these two cursors. Amplitude data were measured using automated detection software to identify peak amplitude and subsequently compared to peak-to-peak latency. Due to the small sample size, statistical comparisons of conditions were not undertaken. However, descriptive statistics were analysed using SPSS statistical software (IBM SPSS Statistics for Windows, Version 21.0, 2012, Armonk, NY: IBM Corp.).

9.3 Results

9.3.1 Healthy Participants

Two participants were unable to sleep with the catheter in situ, but the remaining participants tolerated the procedures and completed the study protocol (n = 20). Average sleep study duration was 7.6 hr (range 6.9–8.2 hr) from positioning the patient supine to the participant waking at the completion of the study. There was an overall swallowing frequency of 5.9 swallows per hour (SD = 3.4; range 1.7–14.9) from a period of one hour following commencement of the sleep study to the participant waking. Any periods of the participant being awake during the night (e.g., needing the restroom) were not included in the frequency analysis. There were no differences between frequency based on the sleep swallow subtype [$F(2,57) = 2.82$, $p = 0.07$]. Average latency and amplitude of pressure across participants is reported in Table 9.2.

Table 9.2 Average amplitude and latency of pharyngeal pressure generation (SD) across healthy participants.

Condition		Amplitude (mmHg)	Latency (ms)	Slope (ms / sensor)
Awake Swallows	Upright	114.1 (± 20.9)	218.8 (± 13.2)	66.5 (± 34.9)
	Supine	113.0 (± 23.2)	204.8 (± 94.0)	58.1 (± 14.2)
Sleep Swallows	Supine	77.9 (± 21.7)	232.2 (± 75.0)	56.9 (± 12.9)

Results indicated no difference between awake upright and awake supine swallowing in terms of amplitude [$t(19) = -3.7$, $p = 0.72$], pharyngeal latency [$t(19) = -0.9$, $p = 0.33$] or slope [$t(19) = -1.3$, $p = 0.21$]. With regard to amplitude, paired t-tests revealed sleep swallows were of significantly lower amplitude than supine awake swallows [$t(19) = 8.1$, $p < 0.01$] as illustrated in Figure 9.2. However, there was no difference between awake supine swallows and supine sleep swallows in terms of latency [$t(19) = -1.7$, $p = 0.11$] or slope [$t(19) = 0.35$, $p = 0.73$].

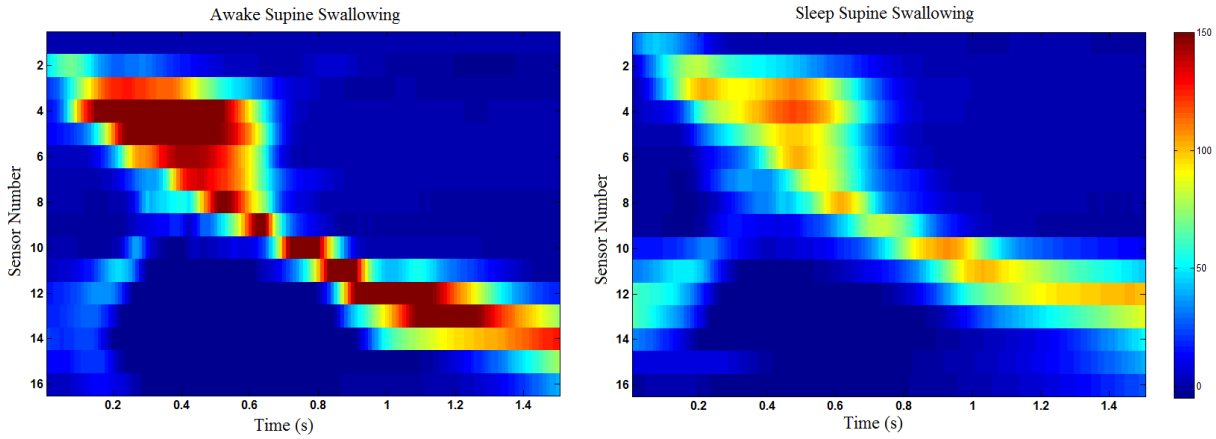


Figure 9.2 These figures represent average sleep and wake pressures. The raw data from supine awake and sleep swallows were exported, averaged and re-plotted to allow direct comparison of multiple swallows between conditions.

Differences across the three sleep swallowing subtypes are reported in Table 9.3 Results from a one-way ANOVA reveal a significant difference in amplitude [$F(2,56) = 13.2$, $p < 0.01$; Figure 9.3], but no differences in temporal measures including latency [$F(2,56) = 0.3$, $p =$

0.77] and slope [F(2,56) = 2.5, p = 0.09]. Tukey post-hoc testing revealed type 1 sleep swallows were lower in amplitude than both type 2 [-36.6 mmHg (95% CI -57.0– -16.1), p < 0.01] and type 3 [-38.2 mmHg (95% CI -58.4– -18.0), p < 0.01], but there was no significant difference in amplitude between type 2 and 3.

Table 9.3 Average amplitude and latency of pharyngeal pressure generation (SD) across sleep swallowing subtypes in healthy participants.

Sleep Swallow Subtype	Amplitude (mmHg)	Latency (ms)	Slope (ms / sensor)
Type 1	51.8 (± 27.1)	183.5 (± 102.5)	56.3 (± 20.0)
Type 2	88.3 (± 25.0)	162.3 (± 102.0)	46.2 (± 15.6)
Type 3	90.0 (± 27.2)	164.8 (± 98.6)	45.4 (± 15.3)

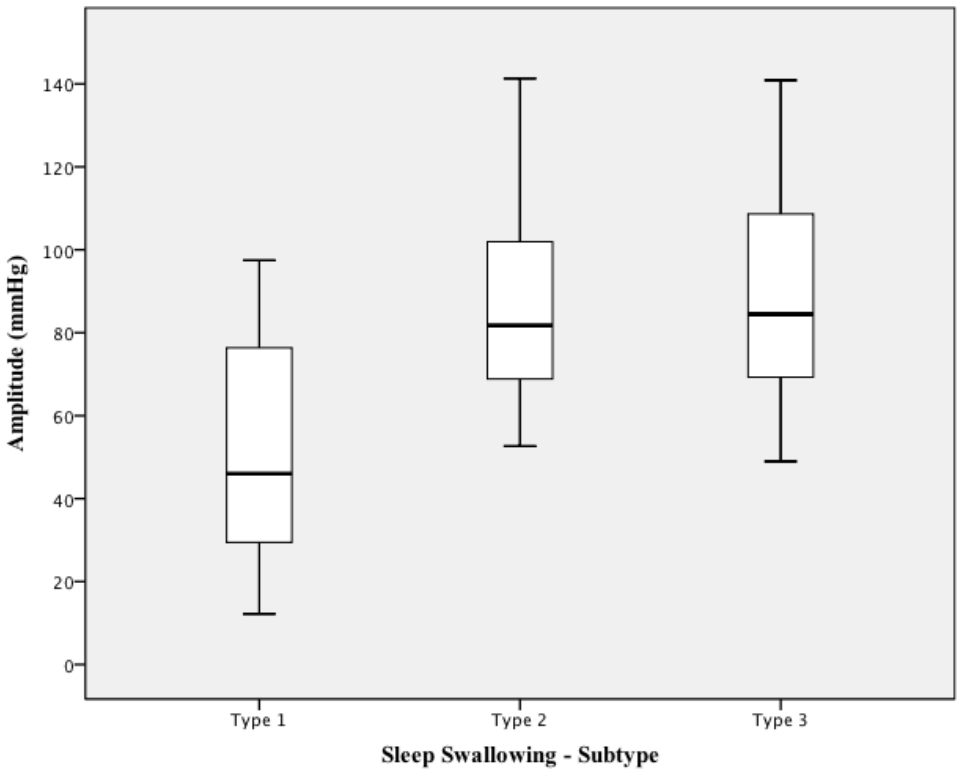


Figure 9.3 Box plot comparing amplitude across sleep swallowing subtypes. The median is represented by the horizontal line, with the box representing the inter-quartile range. The minimum and maximum values are represented by the whiskers.

9.3.2 Patients

All patients tolerated the procedure and completed the study protocol (n = 3). Average study duration was 8.4 hr (range 8–8.9 hr) from positioning the patient supine to the participant waking at the completion of the study. Patients demonstrated a reduction in temporal latency in sleep compared to wake condition, with an average latency of 48.0 ms in supine awake swallowing, reduced to -4.2 ms during sleep (Table 9.4). Amplitude remained markedly low during all conditions, substantially below the 95% confidence interval of normative data (Lamvik et al., 2014).

Table 9.4 Average peak-to-peak latency and amplitude of pharyngeal swallowing immediately prior to and during the sleep study in dysphagic patients.

	Awake Upright Swallows		**Awake Supine Swallows**		**Sleep Swallows**	
	Latency (ms)	Amplitude (mmHg)	Latency (ms)	Amplitude (mmHg)	Latency (ms)	Amplitude (mmHg)
Patient 1	12.0 (± 19.6)	19.7 (± 9.9)	19.8 (± 19.5)	14.1 (± 6.5)	-4.0 (± 3.7)	24.2 (± 19.6)
Patient 2	83.4 (± 5.6)	73.8 (± 26.2)	73.0 (± 46.8)	41.9 (± 27.4)	-0.8 (± 58.2)	39.9 (±26.5)
Patient 3	67.5 (± 91.5)	57.3 (± 13.7)	51.3 (± 84.1)	50.3 (± 26.0)	-7.7 (± 50.3)	30.3 (± 10.6)

9.4 Discussion

This study is the first to characterize differences in wake and sleep swallowing using pharyngeal manometry in healthy participants and patients with dysphagia. Regarding healthy participants, results confirmed with our hypothesis that normal healthy adults will demonstrate significantly lower amplitude of pharyngeal swallowing when asleep. However, results from the temporal analyses revealed no significant differences in latency or slope of pharyngeal pressure. Within the sleep swallowing subtypes, type 1 swallows, with their markedly reduced amplitude, appear characteristic of sleep swallows based on findings from existing literature (Sato & Nakashima, 2006; Sato et al., 2011). Yet, it is unclear how type 2 swallows, consisting of a burst-like pattern not currently reported in the literature, relate to sleep. This swallow subtype may reflect an increased level of arousal, and further research with polysomnographic instrumentation is needed to clearly relate pharyngeal swallowing biomechanics with specific sleep staging. Sleep swallows in the patient cohort present a clear pattern of mis-sequenced pressure, even in the two patients who were able to sequence

pressure adequately to enable functional swallowing when awake, suggesting the need for continued cortical contribution to maintain functional pharyngeal pressure latencies. This contrasts to healthy controls and aligns with patient reports of the need to maintain conscious awareness of swallowing to ensure generalization of gains following rehabilitation.

With regard to methodological aspects of this study, 91% of healthy participants and 100% of patients with dysphagia tolerated the overnight manometric procedure. The two participants unable to complete the study protocol reported difficulty sleeping due to the presence of the intraluminal catheter. In a recent study, Stuckenbrock et al. (2014) evaluated the effect of the presence of a 2-mm catheter on not only procedure tolerability but effect on sleep as measured by polysomnography. Results indicated 80% (n = 51) participants tolerated the sleep study with catheter in situ. Further, of the participants who completed the study, the catheter had no significant effect on the polysomnographic data (Stuckenbrock, Freuschle, Nakajima, & Stuck, 2014). Previous studies report higher tolerability of 87% (n = 107; Virkkula, Silvola, Maasilta, Malmberg, & Salmi, 2002) and up to 96% (n = 799; Oeverland, Akre, Kvaerner, & Skatvedt, 2005). The high compliance found in the present study with a 2.75-mm intraluminal catheter support the findings that most participants are able to tolerate sleep with the catheter in place. Yet, research with larger diameter 4 mm catheters have lower tolerability, reduced to 53% (n = 36; Hessel, Laman, van Ammers, van Duijn, & de Vries, 2003).

Despite tolerability, presence of the catheter may have affected the frequency of swallowing during sleep. Results from the present study indicate an overall frequency of 5.93 swallows per hour (SD = 3.4; range = 1.7–14.9) during sleep. This is comparable with previous studies who reported the average number of swallows per night was 5.8 (range = 2.1–9.1) swallows (Lichter & Muir, 1975). However, our results are higher than recent reports, which indicate 2.9 (SD = 1.3) swallows per hour during sleep in adults and 2.4 (SD = 1.0) in young adults (Sato & Nakashima, 2006; Sato et al., 2011). These studies utilized sEMG to record frequency of swallowing. While the presence of an intraluminal catheter may stimulate swallowing, thereby eliciting a greater frequency of swallows per hour, use of sEMG may underestimate swallowing during the night. Miralles et al. (1998) investigated effects of body position on EMG activity of sternocleidomastoid and masseter muscles in healthy adults (n = 20). Results indicated EMG activities were significantly lower in the masseter muscle in the

supine position (Miralles et al., 1998). Paired with the significant reduction of swallowing amplitude during sleep, sEMG of suprahyoid and thyrohyoid muscles used in work by Sato et al. may not reliably distinguish activation indicative of a swallow from noise in the data at these low amplitudes. Therefore, further research is needed to further understand the relationship between presence of an intraluminal catheter in eliciting higher frequency of swallowing responses, as well as understanding the relationship between sEMG and manometry.

Healthy participants demonstrated no significant difference between upright and supine awake conditions in regard to amplitude or timing measures. This is relevant to use of techniques reliant on supine positioning, such as fMRI. Further studies have reported that supine positioning results in no difference from upright in terms of pharyngeal transit time (Dejaeger, Pelemans, Ponette, & Vantrappen, 1994) and timing and contraction of laryngeal adductor muscles (Barkmeier, Bielamowicz, Takeda, & Ludlow, 2002). However, in a study investigating effects of positioning on pharyngeal swallowing in healthy participants (n = 11), Castell et al. (1990) evaluated differences in pharyngeal pressure between dry and liquid swallows as well as different bolus textures, respectively. Although significant differences existed between wet and dry swallows in the upright and supine position, the same study also documented significant differences between wet and dry swallows in the same position (Castell, Dalton, & Castell, 1990). Therefore, the presence of a bolus appears to impact pharyngeal biomechanics to a greater extent than during dry, spontaneous saliva swallows (Humbert et al., 2009).

The limitations of this study are important to address. Notably, it cannot inform regarding specific sleep stages as techniques such as EEG were not used in the present study. Future studies can elaborate on the present work by directly comparing changes in swallowing biomechanics to sleep staging. Further, a manual correction of measurement error was implemented, which may reduce the accuracy and possibility for replication of the present study. Nevertheless, this study provides early evidence of distinct changes in amplitude of pharyngeal pressure measures when asleep, as compared to wake states, with relative stability of temporal measures. This may provide further information regarding the role of cortical modulation of the pharyngeal swallowing response and provide additional data regarding the debate or the role of volition in swallowing motor control.

Chapter 10: Discussion of Behavioural Studies

The behavioural studies in this thesis assess a continuum of modulation of spontaneous and voluntary swallowing. Initial results from a longitudinal, manofluoroscopic evaluation of a broad neurogenic population led to a series of adjunctive studies, completed to explore mechanisms of pharyngeal mis-sequencing and the nature of underlying neural control of swallowing. Current understanding of central representation of swallowing posits that healthy adults can volitionally modulate amplitude and duration of contraction of the pharyngeal swallow in its entirety (Peck et al., 2010). Contributions to the debate regarding the extent to which humans can volitionally alter discrete sequential elements of the pharyngeal phase of swallowing are discussed below.

Chapter 8 reports findings from the first study which evaluated the capacity of healthy adults to modulate the latency of pressure generation between the proximal and distal pharynx. It can be concluded overall that volitional capability to modulate pharyngeal swallowing is limited to modulation of the overall motor plan, rather than finite elements. While intensive manometric biofeedback training enabled healthy adults to substantially reduce the temporal separation between proximal and distal pharyngeal pressure during volitional swallowing, this was correlated with a contemporaneous change in total swallowing duration and amplitude. Further, the limit in gains suggests that cortical modulation cannot alter the reflexive pharyngeal sequence to a pathologic level. This aligns with existing research indicating healthy adults can volitionally modulate the duration of contraction of the pharyngeal swallow in its entirety (Peck et al., 2010), while the specific timing of individual components in the motor plan for pharyngeal swallowing remains a patterned reflex (Ertekin, 2011). Future studies should further explore the extent to which biofeedback training can be used to investigate the role of volitional control on pharyngeal swallowing. Individualisation of training targets may impact results to show more favourable modulatory capability, as a participant's baseline peak-to-peak latency (e.g., long versus short) could impact the ability to modulate this characteristic of pharyngeal swallowing. This could be expanded in future studies by providing increasingly specific goal-oriented criteria to delineate performance outcomes and effect of biofeedback. In contrast to healthy subjects, it was hypothesize that dysphagic patients would continue to practise the adapted pharyngeal motor plan following

the end of formal biofeedback training and, hence, will further increase, rather than lose, their newly acquired and highly beneficial skill. Successful modulation of the sequence of pharyngeal pressure in patients by cortical voluntary mechanisms would provide evidence to challenge the assumption that the sequence of pharyngeal pressure generation is a fixed and patterned reflexive response, unable to be cortically modulated. This may reflect increases in neural plasticity as a result of neurologic impairment but much research is needed to elucidate this theory (Kleim & Jones, 2008; Joanne Robbins et al., 2008).

In contrast to the evaluation of maximal volitional control, Chapter 9 investigated the characteristic of pharyngeal pressure generation under reflexive conditions. It was unclear if adults presented with a consistent superior to inferior pattern during swallowing when asleep, or if that pattern was present only in volitional prandial ingestion (Huckabee et al., 2014). Thus, this was the first study to characterize differences in wake and sleep swallowing using pharyngeal manometry in healthy participants and patients with dysphagia. Normal healthy adults were found to demonstrate lower amplitude of pharyngeal swallowing when asleep, but no significant differences in timing of pharyngeal swallowing. It is likely the reduction in amplitude in sleep states relates to the marked reduction in salivation during sleep, highlighting the efficiency in the swallowing system (Schneyer et al., 1956). Further, larger volumes of fluid produced a greater number of swallows in NREM sleep, rather than fewer larges swallow responses seen when awake electrodes (Anderson, Dick, & Orem, 1995), highlighting arousal may play an important role in volitional modulation of swallowing magnitude. Similar findings in previous research indicate that patients with neurologic impairment demonstrated a delay in swallowing initiation in response to bolus presentation in the night as compared to when awake (Pinto et al., 1994). Together with findings from Chapter 8, these results provide further evidence that discrete temporal characteristics of pharyngeal swallowing are consistent across volitional and reflexive states, while the amplitude is amenable to alteration across conditions. It is clear that sleep is uniquely suited to investigate reflexive pharyngeal swallowing, as a reduction of volitional control may reduce the influence of cortical modulation. Importantly, therefore, further research is needed with polysomnographic instrumentation (e.g., EEG) is needed to clearly related pharyngeal swallowing biomechanics with specific sleep stages.

Lastly, the results from the behavioural studies provide further evidence regarding the underlying aetiology of pharyngeal mis-sequencing. Sleep swallows in the patient cohort present a clear pattern of mis-sequenced pressure, even in the two patients who were able to sequence pressure adequately to enable functional swallowing when awake (patients 2 and 3), suggesting the need for continued cortical contribution to maintain functional pharyngeal pressure latencies. While this aligns with patient reports of the need to maintain conscious awareness of swallowing to ensure generalization of gains following rehabilitation, it provides preliminary evidence that pharyngeal mis-sequencing may results from the neurologic impairment itself, rather than maladaptive compensation. For example, if pharyngeal mis-sequencing was a result of maladaptive compensation, the impaired pattern would return to a normal sequence when asleep due to reduced supratentorial modulation. However, patient 1, with no rehabilitative gains to date, demonstrated continued mis-sequenced pattern during sleep, similar to patients 2 and 3. It is clear ongoing research described in Chapter 7 may provide further information regarding the underlying aetiology of this atypical presentation of swallowing. However, more comprehensively, analyses of swallowing in sleep may inform us on the role of volition in swallowing motor control. This is of interest when considering possible volitional contributions to pharyngeal swallowing and understanding of pharyngeal swallowing and development of novel rehabilitation protocols.

Across all studies, it is increasingly clear that prior understanding of pharyngeal swallowing as a fixed, reflexive response may be valid to a certain extent. Timing parameters, such as peak-to-peak latency appear consistent despite intensive training and across sleep and wake states, which may be indicative of a basic motor response. However, alterations in amplitude and overall duration of swallowing align with current understanding of ability to volitionally modulate these parameters of pharyngeal swallowing. Changes in amplitude across sleep and wake states highlights this finding. Nevertheless, the execution of the abovementioned behavioural studies identified notable limitations in current diagnostic methods, reducing the reliability and validity with which the rapid sensorimotor swallowing response can be understood. For example, Chapter 9 utilized both low- and high-resolution manometry in evaluation of swallowing function but there is no literature available which has investigated possible differences in measurement of these two techniques. Further, a notable measurement error in HRM was identified, coupled with uncertainty in optimal analysis methods HRM.

Thus, the following chapter provides critical methodological analyses investigating the reliability, validity and measurement accuracy of both low- and high-resolution pharyngeal manometry.

PART II: METHODOLOGICAL STUDIES

Chapter 11: A Comparison of Low- and High-resolution Pharyngeal Manometry

11.1 Introduction

Manometry was originally designed for evaluation of the radially-uniform oesophagus (Dodds et al., 1987). Nevertheless, this instrumentation has been used without adaptation to evaluate the pharynx, vastly different in form and function. As described in Chapter 3, the pharynx has an asymmetrical lumen that constricts and shortens during swallowing. Low-resolution pharyngeal manometry typically has unidirectional, posteriorly-oriented sensors to record timing and amplitude of pressure during swallowing (Salassa et al., 1998). While this design may be appropriate for the uniform peristaltic motion seen in the oesophagus, researchers have questioned the use of unidirectional measurement sensors in the non-uniform pharyngeal lumen (Dodds et al., 1987).

McConnel et al. (1991) evaluated radial symmetry of the pharynx in healthy volunteers (n = 7) using a low-resolution manometric catheter with four solid-state measurement sensors oriented at 90° angles to measure four directions simultaneously. During recording, the catheter was advanced out of the nares at 1 cm intervals, with simultaneous fluoroscopy to monitor catheter placement and bolus flow. Dry swallows and 10 mL liquid barium swallows were recorded (McConnel, Guffin, & Cerenko, 1991). Asymmetry in pharyngeal swallowing was identified, with the greatest asymmetry measured within the UES at rest, and during dry swallows at the level of the base of tongue and hypopharynx. As the asymmetry appeared to be dependent on the presence of a bolus, the authors argued the temporary fluid-filled space created from bolus entry into the pharynx may equalize the radial asymmetry (McConnel et al., 1991). This theory has been postulated in similar research (Brasseur & Dodds, 1991). Inspections of fluoroscopic images reveal greater asymmetry in radial recordings when the catheter deviates from midline position, such as resting on the side of the pharynx. Sears et al. (1991) replicated this study in healthy participants (n = 12) using manometry without adjunctive fluoroscopy. With a similar catheter housing four solid-state measurement sensors oriented at 90° angles, significant radial asymmetry was documented in the distal pharynx, with anterior and posterior pressures significantly higher than lateral pressures (Sears, Castell, & Castell, 1991). The asymmetry varied between 86 ± 13 to 365 ± 29 in lateral and posterior directions, respectively (Castell & Castell, 1993; Sears et al., 1991). The authors

concluded that awareness of sensor location and orientation was essential for accurate and reliable evaluation of pharyngeal pressure.

To date, the literature has suggested that use of circumferential sensors may be beneficial by averaging pressure radially, thereby overcoming limitations in unidirectional measurement (Salassa et al., 1998). However, significant differences have been identified between unidirectional and circumferential sensor recordings in the LES (Pursnani, Oeffner, Gideon, & Castell, 1997). This has been considered to be a byproduct of increased catheter diameter, as circumferential sensors contribute to an increased catheter width from 2.1 mm to up to 6 mm (Salassa et al., 1998). However, a recent study compared circumferential measurements of HRM with unidirectional measurements of a novel 'unisensor' catheter called 'Starlet' (Kuribayashi et al., 2015). While the pressures measured by Starlet were significantly higher than pressures recorded in the circumferential HRM system, the Starlet catheter had an increased diameter of up to 5.4 mm (compared to the 4.2 mm HRM catheter; Kuribayashi et al., 2015). It was therefore not clear if the pressure differences were due to the measurement characteristic or the catheter diameter. In comparing low-resolution manometric data using a 2.1 mm catheter to HRM data using a 4.1 mm catheter, normative data varies markedly. For example, in young males, low-resolution manometry revealed a pharyngeal composite amplitude (average of tongue base pressure and hypopharynx) of 118.5 mmHg (105.2 – 131.8; Lamvik et al. 2014) while in HRM, meso-hypopharyngeal amplitude (average of tongue base pressure and hypopharynx) was 175.3 mmHg (115.6 – 235; Takasaki et al., 2008). However, inherent in this difference is catheter diameter, as circumferential sensors contribute to a larger catheter diameter than unidirectional sensors.

With recent advances in the design of circumferential sensors, paediatric HRM catheters are now available at 2.75 mm diameter. Thus, direct comparison of unidirectional and circumferential sensors of similar diameter is now feasible. Therefore, this exploratory study evaluated timing and amplitude of swallowing pressure by comparing unidirectional, low-resolution manometry to circumferential HRM. It was first hypothesized that no significant differences would be identified in the peak or nadir amplitude between the two sensor types (unidirectional versus circumferential). This study is paramount to understand differences between these two solid-state recording sensors, which may clarify variability in existing normative data.

11.2 Materials and Methods

11.2.1 Participants

Ten healthy participants (3 females), ranging in age from 21 – 35 years (mean 29 years) participated in the study. No participant reported a history of dysphagia, neurological or muscular impairment, or use of any medications that might have affected swallowing. Ethical approval was obtained from the local institutional review board and informed consent was obtained from all participants prior to commencement of data collection.

11.2.2 Equipment

A 100 cm long catheter, 2.1 mm in diameter (Model CTS3 + EMG, Gaeltec, Hackensack, NJ, USA), was used for manometric data collection. As per standardized catheter recommendations from Salassa, DeVault, & McConnel (1998), the catheter housed 3 solid-state, unidirectional, posteriorly-oriented sensors (2 x 5 mm) with 2 cm spacing between sensors 1 and 2, and 3 cm between sensors 2 and 3. Pressures were measured at the proximal pharynx, distal pharynx and UES with sensors 1, 2 and 3 respectively. The catheter was connected to the Kay Elemetrics Digital Swallowing Workstation (Model 7120, Kay Pentax, Lincoln Park, NJ, USA), with digitized recording of pressure waveforms as a function of time displayed in real time in a -100 to 500 mmHg display window on a computer screen and digitally recorded for offline analysis. High-resolution manometry studies were completed using the ManoScan 360™ High-resolution Manometry system (Model A120) with a paediatric ManoScan™ ESO catheter (EPS0042) containing 36 pressure sensors at 2.75 mm diameter. In-vivo calibrations were routinely performed and each recording session was preceded by calibration per standard operating instructions. All studies were corrected for thermal effect measurement error with application of a standard 'Thermal Compensation' correction method, as recommended in the user guide.

11.2.3 Procedures

All participants were seen for two sessions: evaluation with low-resolution manometry and evaluation with HRM. The order of the circumferential versus unidirectional catheter placement was counter-balanced into two equal groups between session one and session two.

Low-resolution Manometry

The low-resolution manometric catheter was inserted into one naris, using routine clinical and research protocols, detailed in Chapter 7 and 8. Posterior orientation of the three sensors was confirmed by monitoring unidirectional markers on the catheter. At final placement, sensor 1 was located in the proximal pharynx (approximately at the level of the base of tongue), sensor 2 in the distal pharynx (approximately at the level of the laryngeal additus) and sensor 3 in the proximal aspect of the UES. The insertion depth was recorded for subsequent comparison to HRM catheter placement.

Each subject was asked to perform five dry swallows at a self-generated pace, approximately one swallow every minute to record baseline function. Sips of water were offered as needed to moisten the mouth. Then, the participants were asked to perform twenty 10 mL thin liquid bolus swallows (water), at their own pace, typically one swallow every 30 s. Five swallows were completed in each direction, with the unidirectional catheter repositioned by rotating 90° at the level of the nares. Rotational stability has been found to be robust with standard ovoid catheters used in the present study, validated previously against VFSS (Salassa et al., 1998). Throughout data collection, evaluation of manometric waveforms by the researcher ensured correct placement was maintained. The same protocol of five dry swallows and five 10 mL liquid swallows was repeated at four directions, including poster, left, anterior and right.

High-resolution Manometry

The HRM catheter was placed transnasally using a routine protocol, detailed in Chapter 9. The catheter was inserted until sensor 1 was located just inside the naris with sensor 36 in the cervical oesophagus, enabling the length of the upper aerodigestive tract to be evaluated in its entirety. Each subject was then asked to perform five dry swallows at a self-generated pace, approximately one swallow every minute to record baseline function. Sips of water were offered as needed to moisten the mouth. Then, the participant was asked to drink five 10 mL thin liquid bolus swallows (water), at their own pace, typically one swallow every 30 s. The catheter was then removed and data collection was completed.

11.3.4 Data Analysis

Depth of insertion was compared for low-resolution and HRM catheters to align sensors and enable direct comparison of measurement. Thus, the only sensors measured from the HRM system were three sensors that directly corresponded to the low-resolution manometric catheter sensors 1, 2 and 3. This allowed individualisation in comparison of data, as differences in height and structural anatomy can lead to differences in sensor location within the pharynx across individuals (Salassa et al., 1998).

Swallowing data were measured off-line for each subject using the Kay Digital Swallowing Workstation software for low-resolution manometric data and the ManoView^{TM} software for HRM data. In both software platforms, temporal values were measured with manually placed, digital cursors for peak latencies of pharyngeal pressures generated at sensors 1 and 2 with peak-to-peak latency calculated as the difference between these two cursors. Total swallowing duration was measured from onset of pressure at sensor 1 to the offset of pressure at sensor 2. Duration of UES relaxation was measured from the peak pressure prior to relaxation, to post-relaxation return to pressure at the completion of the swallow. Amplitude data were measured using automated detection software to identify nadir amplitude in the pharyngeal sensors and UES.

Comparisons were made across the four measurement directions of low-resolution manometry to analyse radial asymmetry within unidirectional low-resolution manometry. Radial asymmetry was evaluated using a repeat-measures ANOVA with post-hoc testing, as appropriate. Then, a second comparison was completed between low- and high-resolution manometry, comparing conventional, posterior-recording to HRM as well as an average of the four unidirectional recording directions (e.g., approximated, composite circumferential) to HRM measures of corresponding sensors within each participant. Comparisons between low- and high-resolution manometry measures were made with paired-samples t-tests between averages of low-resolution manometry data in conventional posterior direction with HRM, as well as low-resolution manometry data averaged across the four measurement directions with HRM. Data were analysed using SPSS statistical software (IBM SPSS Statistics for Windows, Version 21.0, 2012, Armonk, NY: IBM Corp.).

11.3 Results

All participants completed the protocol without adverse event. Participants had an average catheter insertion distance of 23.4 cm (SD = 1.4) on low-resolution manometry from the nares to the tip of the catheter in the distal oesophagus.

11.4.1 Radial Symmetry

Descriptive statistics for measurement of the four radial directions with the low-resolution manometric catheter are reported in Table 11.1. Results from repeat-measure ANOVA revealed no significant difference as a result of recording direction for amplitude in sensor 1 [dry swallow - $F(3, 27) = 0.5$, $p = 0.71$; liquid swallow - $F(3, 27) = 1.18$, $p = 0.44$], sensor 2 [dry swallow - $F(3, 27) = 2.1$, $p = 0.13$; liquid swallow - $F(3, 27) = 1.2$, $p = 0.34$] or the UES [dry swallow - $F(3, 27) = 1.6$, $p = 0.20$; liquid swallow - $F(3, 27) = 0.5$, $p = 0.68$]. Temporal results were similar with no significant difference as a result of recording direction for swallowing duration [dry swallow - $F(3, 27) = 0.7$, $p = 0.56$; liquid swallow - $F(3, 27) = 0.3$, $p = 0.86$], peak-to-peak latency [dry swallow - $F(3, 27) = 0.1$, $p = 0.95$; liquid swallow - $F(3, 27) = 0.4$, $p = 0.78$] or UES nadir duration [dry swallow - $F(3, 27) = 0.6$, $p = 0.63$; liquid swallow - $F(3, 27) = 1.5$, $p = 0.23$].

Table 11.1 Average (SD) temporal latencies (ms) and amplitude (mmHg) across the four radial measurement directions during dry swallowing.

	Latency			**Amplitude**		
	Swallowing Duration	Peak-to-Peak Latency	UES Nadir Duration	Sensor 1	Sensor 2	UES Nadir
Posterior	835.1 (294.5)	231.8 (99.8)	1196.7 (418.7)	111.1 (27.8)	139.2 (50.4)	-17.6 (10.4)
Left	748.4 (245.5)	231.5 (89.9)	1127.6 (366.2)	100.2 (33.7)	121.5 (55.5)	-16.0 (14.5)
Anterior	782.4 (264.9)	234.0 (72.2)	1135.3 (279.1)	107.1 (36.2)	125.2 (46.8)	-13.3 (15.1)
Right	751.8 (306.0)	220 (107.0)	1225.8 (234.6)	107.1 (36.2)	117.3 (40.7)	-13.7 (14.3)

11.3.2 Comparison of unidirectional and circumferential measures

Paired t-tests were used to compare low- and high-resolution manometry temporal and amplitude measurements for dry and liquid swallowing. HRM was compared with

conventional posterior orientation of low-resolution manometry (Table 11.2), as well as an average of low-resolution manometric data across the four directions (Table 11.3), mimicking circumferential measurement with the low-resolution manometry unidirectional sensor. There were differences in peak-to-peak latency between both unidirectional measurement methods and HRM in dry swallowing, with no significant differences in peak-to-peak latency in liquid swallowing. Amplitude was lower in averaged low-resolution manometry as compared to HRM in dry and liquid swallowing conditions.

Table 11.2 Average temporal latencies (ms; SD) in dry and liquid swallowing conditions, as compared between low- and high-resolution manometry.

	Dry Swallows			**Liquid Swallows**		
	Swallowing Duration	Peak-to-Peak Latency	UES Nadir Duration	Swallowing Duration	Peak-to-Peak Latency	UES Nadir Duration
Posterior Low-resolution Manometry	835.1 (294.5)	231.8 (99.8)	1196.7 (418.7)	638.1 (162.3)	263.9 (154.6)	1193.6 (282.5)
*Sig. (*p <0.05)*	0.61	0.05*	0.12	0.04*	0.68	0.02*
High-resolution Manometry	866.2 (251.7)	262.6 (77.5)	1380.0 (260.0)	776.7 (243.4)	248.2 (78.5)	1486.0 (408.9)
*Sig. (*p <0.05)*	0.16	0.05*	0.02*	0.07	0.96	0.09
Averaged Low-resolution Manometry	779.3 (245.7)	229.0 (77.8)	1171.0 (285.1)	669.2 (207.5)	249.6 (75.5)	1336.6 (356.6)

Table 11.3 Average amplitude (mmHg; SD) across dry and liquid swallowing conditions, as compared between low- and high-resolution manometry.

	Dry Swallows			**Liquid Swallows**		
	Sensor 1	Sensor 2	UES Nadir	Sensor 1	Sensor 2	UES Nadir
Posterior Low-resolution Manometry	111..7 (35.5)	146.3 (53.0)	-17.6 (10.4)	111.1 (27.8)	139.2 (50.4)	-13.5 (13.8)
*Sig. (*p <0.05)*	0.20	0.37	0.02*	0.41	0.00*	0.20
High-resolution Manometry	122.0 (37.8)	161.2 (55.7)	-4.9 (4.2)	122.6 (35.0)	174.6 (45.9)	-6.4 (2.9)
*Sig. (*p <0.05)*	0.01*	0.02*	0.08	0.03*	0.00*	0.32
Averaged Low-resolution Manometry	101.3 (26.4)	126.1 (43.1)	-15.2 (13.0)	101.9 (25.9)	126.9 (41.7)	-12.4 (15.1)

11.4 Discussion

With the advent of technological improvements in instrumentation, there appears to be a tendency to rapidly integrate novel tools prior to systematically comparing to older systems. This is worrying as it may inhibit a thorough understanding of relative strengths and weaknesses of novel instrumental techniques as compared to existing tools. With regard to manometry, despite the wide-spread use of HRM following its development, this is the first study to compare low- and high-resolution manometry within subjects. The findings of the present study are critical in order to understand notable differences in normative data between low- and high-resolution manometry. Importantly, there were significant differences in the measurement of peak-to-peak latency in dry swallowing conditions between low- and high-resolution manometry, both when using posteriorly-oriented, unidirectional measurement or when averaging the low-resolution manometry data to approximate a circumferential recording. Further, there were significant differences between the duration of UES relaxation between conventional posteriorly-oriented low-resolution manometry to HRM in liquid swallowing and with averaged low-resolution radial pressures and HRM in dry swallowing. This can affect clinical practice and research of dysphagia as it becomes unclear which tool provides increasingly accurate results.

The differences seen between measurements in low- and high-resolution manometry contrasts to consistency in radial symmetry. Results indicate low-resolution manometry demonstrates

consistent recording across directions with no significant differences in magnitude or temporal parameters. This contrasts to prior research, which may reflect differences in catheter types (McConnel et al., 1991; Sears et al., 1991). In both prior studies who demonstrated intraluminal radial asymmetry, they used non-standard catheters custom-built for the study. However, the results of the present study are derived from use of a standardised catheter, which may enable generalisation of results to improve understanding practical use of this technique. It appears unlikely that small differences in catheter direction orientation will affect pressure measurement based on the present results. Yet, though there is no significant difference in radial symmetry within the low-resolution manometry catheter, there remains a difference between this measure to the circumferential measurements obtained from the HRM catheter. This highlights the potential for extraneous factors, such as tendency toward measurement artefact, guiding the need for further research comparing differences in these two similar intraluminal pressure measurement devices.

Manometry is uniquely position to evaluate UES function due to its objectivity and high temporal resolution (Jones et al., 2014; Jones, Hammer, et al., 2014; Knigge et al., 2014). However, HRM appears to identify a significantly longer UES relaxation duration than low-resolution manometry, at a higher amplitude within the same subjects, in liquid swallowing. This is apparent when comparing existing normative data. Low-resolution manometry revealed a pharyngeal composite amplitude (average of tongue base pressure and hypopharynx) of 118.5 mmHg (105.2 – 131.8) in young males (Lamvik et al. 2014), which is lower than the same measure recorded with HRM (175.3 mmHg, 115.6 – 235; Takasaki et al., 2008). Further research is needed with adjunctive imaging instrumentation, such as simultaneous VFSS, to characterize these differences in manometric pressure recordings.

The radial symmetry documented in the present study is at odds with prior research. While previous literature denies asymmetry with the presence of a bolus, similar to the present study, McConnel et al. (1991) found asymmetry during rest in the UES and during dry swallows at the level of the base of tongue and hypopharynx. Further, Sears et al. (1991) found significant radial asymmetry in the distal pharynx, with anterior and posterior pressures significantly higher than lateral pressures. These differences may relate to instrumentation used, as both studies above used non-standard, custom-built catheters. Further, it is unclear why there is radial asymmetry in dry swallowing, but not bolus swallowing. Both authors

posit that when a bolus fills the cavity, it equalizes pressure recorded on any given sensor. However, it is unclear why a bolus would result in such notable differences, as both dry and liquid swallows occur with contemporaneous maximal occlusion of the lumen. Further research is needed to investigate this further, especially across varied bolus sizes and consistencies if the presence of a bolus indeed affects radial symmetry. The abovementioned studies used four unidirectional sensors recording each direction simultaneously. In the present study, unidirectional sensor orientation was based on catheter rotation, which may have led to inaccuracy in placement. However, rotational stability has been found to be robust with standard ovoid catheters used in the present study (Salassa et al., 1998). As stated above, replication with simultaneous imaging is needed to confirm sensor orientation. Nevertheless, present results indicate that small alterations in sensor recording direction may have minimal effect in measurements of timing and magnitude of pharyngeal pressure.

The present study is not without limitations. While the low- and high-resolution catheters were of similar diameter, they were not identical at 2.1 mm and 2.75 mm, respectively. The larger HRM catheter was found to have higher amplitude and longer duration of UES relaxation. This is consistent with research indicating similar changes in swallowing biomechanics are evident during ingestion of larger boluses, potentially mimicked with the presence of a larger catheter (Kahrilas et al., 1988). Yet, it is unclear if a difference of 0.65 mm is substantial enough to have an effect on swallowing biomechanics. Further, although there were no statistical significance regarding radial asymmetry, this may as well result from the large standard deviations around the mean, indicating substantial variability across and within each recording direction. The direction was not randomized across participants, which may lead to bias relating to trial effect. While this may result from inaccuracies in positioning the sensor in each radial direction, further research is needed to elucidate this point. An unequal number of trials were completed across low- and high-resolution manometry, namely 5 and 20 trials, respectively. A larger study with a greater number of participants may aid in characterizing differences in recording and contribute to statistical interpretation of differences between the radial directions.

Nevertheless, it appears that low- and high-resolution manometry may be uniquely suited to measure contrasting characteristics, with low-resolution manometry demonstrating differences in measurement of peak-to-peak latency, while HRM may be increasingly

appropriate for evaluation of UES dysfunction. While HRM has largely replaced low-resolution manometry, there may be a continued place for use of low-resolution manometry in the evaluation of swallowing, especially while HRM undergoes more rigorous testing of reliability and validity discussed subsequently. The differences in measurement may as well relate to a lack of consensus in measuring pharyngeal spatiotemporal plots from HRM examinations to date. While HRM remains superior in spatial resolution, managing and interpreting the large quantities of data generated from a routine clinical examination may limit the applicability of this technique at present. The subsequent chapters will discuss this issue to a greater degree.

Chapter 12: Characterization and Correction of Measurement Error in Low- and High-resolution Manometry: In-Vitro and In-Vivo[10]

12.1 Introduction

As discussed in Chapter 4, establishing the reliability and validity of a measurement tool is critical for accurate diagnostics of oropharyngeal swallowing. While the advent of HRM has improved upon limitations of low-resolution manometry, this novel technique has not been evaluated in terms of reliability and validity. This is critical as a marked measurement error, described in Chapter 9, had been identified but insufficiently characterized to date. Further, while data presented in this thesis do not indicate a similar measurement error in low-resolution manometry, this has not been systematically evaluated.

The only report of manometric measurement error in the literature relates to the ManoScan™ system. This system is used widely in research (Hammer et al., 2009; Hoffman et al., 2012; Jones et al., 2015; Knigge et al., 2014; Lee et al., 2014; Mielens et al., 2012; Nativ-Zeltzer et al., 2012; O'Rourke et al., 2014; Takasaki et al., 2011) and in the present work. Although the measurement error is pronounced in extended duration recordings, this phenomenon is reported in only two published manuscripts (Babaei et al., 2015), one published abstract (Babaei et al., 2015) and one technical note (Robertson et al., 2012). This measurement error reportedly consists of a substantial drift in pressure, refuting the manufacturer's report of pressure uniformity remaining within 2 mmHg for 4 or less hours of recording (Babaei, Lin, et al., 2015; Robertson et al., 2012). This deviation in pressure can profoundly impact interpretation of existing normative data as well as render existing protocols for use of manometry in clinical settings inappropriate without optimal data correction (Knigge et al., 2014). While it is well established that this drift is considerable, variable and not corrected by standard operating instructions, three fundamental questions remain insufficiently answered.

First, what is the pattern of drift within and across studies? Although it is clear that drift is present, there are conflicting reports on the pattern of this drift. Robertson et al. (2012) evaluated drift in-vitro, using a water bath of known depth during 2 hr recordings. The

[10] The content contained in this chapter was published as Lamvik, K., Guiu-Hernandez, E., Jones, R., Huckabee, M-L. (In Press). Characterization and correction of pressure drift in the ManoScan™ high-resolution manometry system: In-vitro and in-vivo. Neurogastroenterology and Motility.

authors identified two components in pressure drift: a 'thermal effect,' defined as an immediate change in pressure as the catheter temperature changes to body temperature at intubation and a 'baseline drift,' which represents a linear drift across time. In one of their analyses, Babaei et al. (2015) evaluated drift in-vivo by monitoring the first pharyngeal sensor from a large dataset of 560 clinical studies recorded by six distinct HRM catheters. The authors simply reported that the pressure drift is "variable throughout the recording, even in the pharynx" (Babaei et al., 2015; p. 283).

Second, what components contribute to drift? Although Robertson et al. (2012) found the thermal effect to result from temperature shock, they stated that 'baseline drift' is directly related to study duration, increasing with a linear trajectory. In contrast, Babaei et al. (2015) concluded "contrary to common perception, temperature, duration and even peak pressure exposure are not the principal determinants of variable [pressure drift] across sensors of a clinical manometry study" (p. 283). They speculated that average pressure exposure on a sensor was the most influential factor in predicting pressure drift. However, they did not report if they removed drift from average pressure exposure before correlating the average pressure with drift. This has the potential to greatly bias results. Further, with an average recording duration of 35 min (±14 min), it is unclear if study durations were sufficient to reveal additional baseline drift.

Thirdly, how do the available correction methods operate and perform? Both articles reported that thermal compensation (TC) does not sufficiently address the drift; however, neither study used the ManoView™ analysis software to apply TC. Additionally, Robertson et al. (2012) replicated a second correction method (activated in the software following discussion with the manufacturer), termed interpolated thermal compensation (ITC) with a manual compensation algorithm. As above, the accuracy and generalisability of their manual replication of this secondary analysis method is unknown.

The aim of the present study was to explore these three questions in-vitro and in-vivo, both in abbreviated and extended-length recordings of low- and high-resolution manometry. Although in-vitro studies have been criticized in previous reports (Babaei et al., 2015), a controlled environment is robust for investigating system faults. This study is the first to analyse drift both in-vitro and in-vivo in low- and high-resolution manometry, as well as the

first to evaluate correction methods using the ManoView™ analysis software. This is important for both clinical use and future research of manometry.

12.2 Materials and Methods

12.2.1 Participants

Participants (n = 20) ranged in age from 21–52 yr (mean = 32.3 yr). No participant reported a history of dysphagia, neurologic disorder, or muscular impairment. No participant reported use of any medications that are known to affect swallowing or sleep. Ethical approval was obtained from the local institutional review board with informed consent obtained prior to commencement of data collection.

12.2.2 Equipment

Low-resolution manometry studies were completed using a 100-cm-long catheter, 2.1 mm in diameter (Model CTS3 + EMG, Gaeltec, Hackensack, NJ, USA). As per standardized catheter recommendations from Salassa, DeVault, & McConnel (1998), the catheter housed 3 solid-state, unidirectional, posteriorly-oriented sensors (2 x 5 mm) with 2 cm spacing between sensors 1 and 2, and 3 cm between sensors 2 and 3. The catheter was connected to the Kay Elemetrics Digital Swallowing Workstation (Model 7120, Kay Pentax, Lincoln Park, NJ, USA), with digitized recording of pressure waveforms, recorded for offline analysis.

HRM studies were completed using the ManoScan 360™ High-resolution Manometry system (Model A120) and combined ManoScan Z™ system (Model A200). Two catheters were tested as part of this protocol: (1) ManoScan™ ESO catheter (EPS0042) with 36 pressure sensors at 2.75 mm diameter and (2) ManoScan™ ESO Z catheter (EAZ1523) containing 36 pressure sensors and 18 impedance channels at 4.2 mm diameter. Both catheters were free from defect and under warranty, with 169 and 33 uses for the ESO and ESO Z catheters, respectively. In-vivo calibrations were routinely performed and each recording session was preceded by calibration per standard operating instructions.

12.2.3 Procedures

Low-resolution Manometry

Two 8 hr in-vitro studies were performed in a water bath at 37°C and at a depth of 4.0 cm (equivalent to 2.9 mmHg). The temperature of the water bath was maintained with a digital

immersion circulator and manually confirmed by the researchers with an external digital thermometer each hour.

High-resolution Manometry

Eight 15 min and nine 8 hr in-vivo studies were performed with healthy participants using the ESO catheter. For the 15 min in-vivo studies, data were collected on volitional and spontaneous swallowing, with five cued dry swallows and five 10 mL thin liquid bolus swallows in 15 min (in addition to spontaneous swallowing generated by the participant). Data for the extended length studies were collected overnight. The catheter was placed transnasally using a routine protocol, delineated in Chapter 9. As this research study investigated pharyngeal rather than oesophageal swallowing, sensor 1 was located just inside the naris. The participant was assisted to achieve a comfortable position in bed following catheter insertion and was allowed to sleep. The researchers monitored the participant through observation of manometric recordings throughout the night, viewed via remote access to the HRM system. Approximately 8 hr from intubation, the catheter was removed from the nasopharynx.

Eight 15 min and six 5 hr in-vitro studies were performed in a water bath at 37°C at a depth of 4.0 cm (equivalent to 2.9 mmHg). These short and long duration in-vitro studies were replicated with both the ESO and ESO Z catheters, for a total of sixteen 15 min studies and twelve 5 hr studies at a depth of 4.0 cm. An additional six 5 hr studies were completed with the ESO Z catheter at an increased depth of 9.0 cm (equivalent to 6.6 mmHg). All 5 hr in-vitro studies included a 2 min initial 37°C water bath, after which the catheter was held aloft in room-temperature air for 30 sec, prior to re-immersion into the 37°C water bath for the 5 hr recording period. The temperature of the water bath was maintained with a digital immersion circulator and manually confirmed by the researchers with an external digital thermometer each hour.

12.2.4 Compensation Methods

The manufacturer provides a standard TC method in the analysis software. TC is a single-step process where the user applies the correction method at a manually selected time point following extubation. The time point is selected based on user manual recommendations to select the point as close as possible following extubation when no pressure is applied on the

catheter. This allows evaluation of the catheter at body temperature, before the catheter cools to room temperature. Since there is no external pressure applied at this time point, the recorded pressure on each sensor can then be subtracted from the entire recording from each respective sensor. The manufacturer recommends applying this TC to all studies prior to analysis.

ITC, a compensation method developed to compensate for longer duration studies, is not enabled by default in the software and requires manufacturer intervention for use. ITC is executed by selecting two time points with no external pressure applied, one at the beginning and one at the end of the study, which are set to 0 mmHg. According to the application note, drift between these two points is then corrected with linear interpolation. To achieve this, it is necessary to prepare a water bath at 37°C. At the beginning of the recording, the catheter is immersed in this water bath for a period of 2 min. The catheter is then removed and held aloft at room temperature air with no external pressure applied. Intubation is then performed during continuous recording. At the end of the study, the user continues to record pressure during extubation, as done for the TC method. Thus, pressure is continually recorded from the point of immersion in the initial water bath to extubation at completion of the study. A two-step process in the ManoView™ software environment is used to compensate the data. First, TC is applied at the user-selected time point at catheter removal from the initial 2 min water bath to remove any thermal effects. Then, ITC is applied at the user-selected time point immediately following extubation at the end of the study to correct for drift.

12.2.5 Data Analysis

Low-resolution Manometry

Amplitude data were measured using automated detection software to identify average baseline amplitude. Ten samples were taken each hour, averaged to create a mean baseline pressure amplitude across the 8 hr recordings.

High-resolution Manometry

Pattern of drift

To investigate the first question regarding the pattern of drift within and across studies, only the extended-duration studies were evaluated. Raw data from the in-vivo studies were exported and plotted using commercial software (MATLAB R2014a, The MathWorks Inc.,

Natick, MA, 2014). A best-fit line approach was utilized to allow filtering of swallowing-related pressure from overall pressure recording during the extended duration in-vivo studies. This best-fit line was generated for each sensor from a time point 2 min from the start of the study (when any thermal effect would be stabilized; Robertson et al., 2012), to 2 min from the end of the study (prior to extubation). A median across 10 samples at each time point was used to ensure the point selected was representative of recorded pressure at the start and end of the study. Baseline drift per hour was then calculated by subtracting the first point (median of 10 samples) of the best fit line from the last point (median of 10 samples) and dividing by study length in hours. Thermal effect was estimated by subtracting the total baseline drift from the last point, with any residual pressure constituting a thermal effect.

The controlled 5-hr in-vitro studies were evaluated in a two-step manner. First, raw pressure data after catheter removal from the 2-min water bath was analysed to evaluate thermal effects. The time point for analysis was manually selected and corresponded to the time of removal of the catheter from the water bath, leaving the catheter at 37°C but with no external pressure applied (as specified in the user manual). Any incident pressure above zero was attributed to a thermal effect. These pressures were then corrected using the first step of the ITC process on the standard ManoView™ analysis software. Similar to in-vivo studies, a best-fit line was generated to calculate baseline drift per hour. Additionally, linearity of baseline drift was evaluated for goodness of fit, comparing results to the best-fit line.

Non-parametric statistics were necessary due to highly non-normal distributions of the pressure data (Shapiro-Wilk test, $p < 0.01$). A median was calculated to represent overall drift, baseline drift per hour and thermal effect for each study. This comprised a median across the 36 sensors for each individual study. Maximum drift per hour and inter-quartile range (IQR) were also calculated. Kruskal-Wallis H tests were used to evaluate the variability across sensors and studies. A Wilcoxon Signed-Rank Test was used to compare thermal effect and baseline drift per hour, respectively, between in-vivo and in-vitro data. Of note, sensor 27 in the ESO catheter was found to have values consistent with extreme outliers in the extended duration studies. This sensor was removed from analyses but reported separately when applicable (see Table 2).

Origin of Drift

A Pearsons product-moment correlation coefficient was used to analyse the relationship between thermal effect and baseline drift per hour. With regard to the in-vivo studies, mean and maximum pressures on each sensor were calculated for the 15-min studies. Pearsons product-moment correlation coefficients were again used to analyse the relationships between average and maximum pressure exposure with overall drift, both before and after correction. A Wilcoxon Signed-Rank Test was used to compare overall drift, thermal effect and baseline drift per hour, respectively, between the low (4 cm water) and high (9 cm water) depth studies.

Correction Methods

Finally, TC was applied using the ManoView™ analysis software for the 15 min studies and both TC and ITC were applied to the 5 hr in-vitro studies based on methods specified in the user manuals. Performance of correction methods were evaluated from the in-vitro water bath recordings as this allows direct comparisons from the corrected pressure readings to the known pressure applied, namely 2.9 mmHg. For the 15 min in-vitro studies, the error was calculated by subtracting 2.9 mmHg from the recorded pressure at each sample across the 15 min period. Next, a median was taken from these results to represent the study error in its entirety. Then, from the raw data, TC was applied and medians were re-computed with the same method to compare error of this compensation method to the raw data. A similar method was utilized for the extended duration studies. The error was calculated by subtracting 2.9 from the recorded pressure at each sample across the 5 hr period. Median error over time was then calculated by generating the median of all the sample errors across 30 min, 2 hr, 4 hr and at the end of the study, respectively. The median error of the raw data was then compared to the error resulting following application of TC or ITC. A schematic of the data analysis methods are depicted in Figure 12.1.

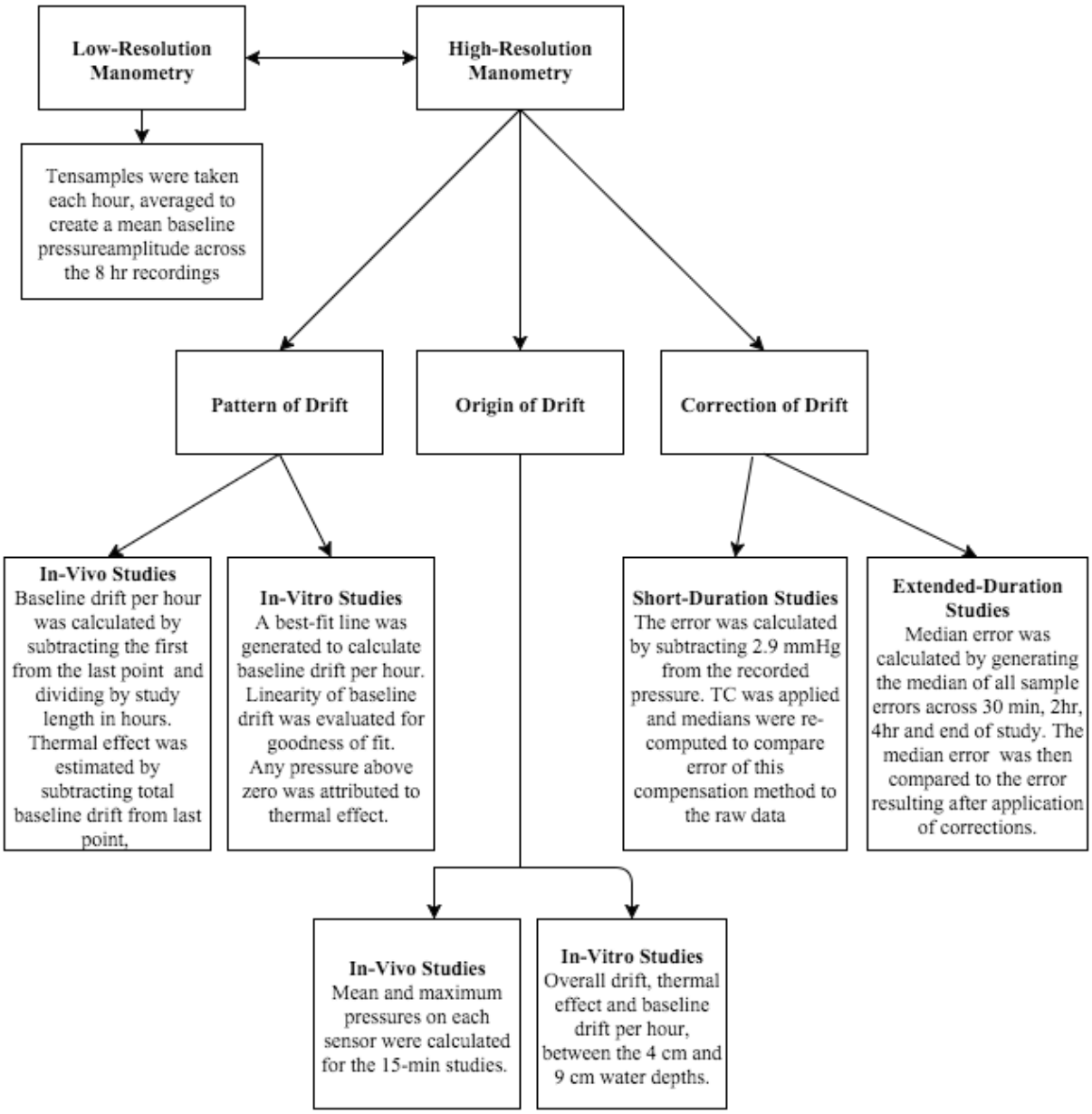


Figure 12.1 Flow-chart analysis methods used in the present study across low- and high-resolution manometric investigations.

12.3 Results

12.3.1 Low-resolution Manometry

Low-resolution manometric studies were highly consistent across recording, with all measures within 3 mmHg. Sensor-specific variability across the in-vitro studies are reported in Table 12.2 and pressure averages across each hour are depicted in Figure 12.1. Of note are the narrow standard deviations, less than 0.5 mmHg across all sensors.

Table 12.1 Average baseline pressure (mmHg) across low-resolution manometry in-vitro studies.

	Sensor 1	Sensor 2	Sensor 3
Study 1	2.3 (0.3)	-1.0 (0.3)	-2.6 (0.3)
Study 2	2.4 (0.1)	-2.4 (0.1)	-2.4 (0.1)

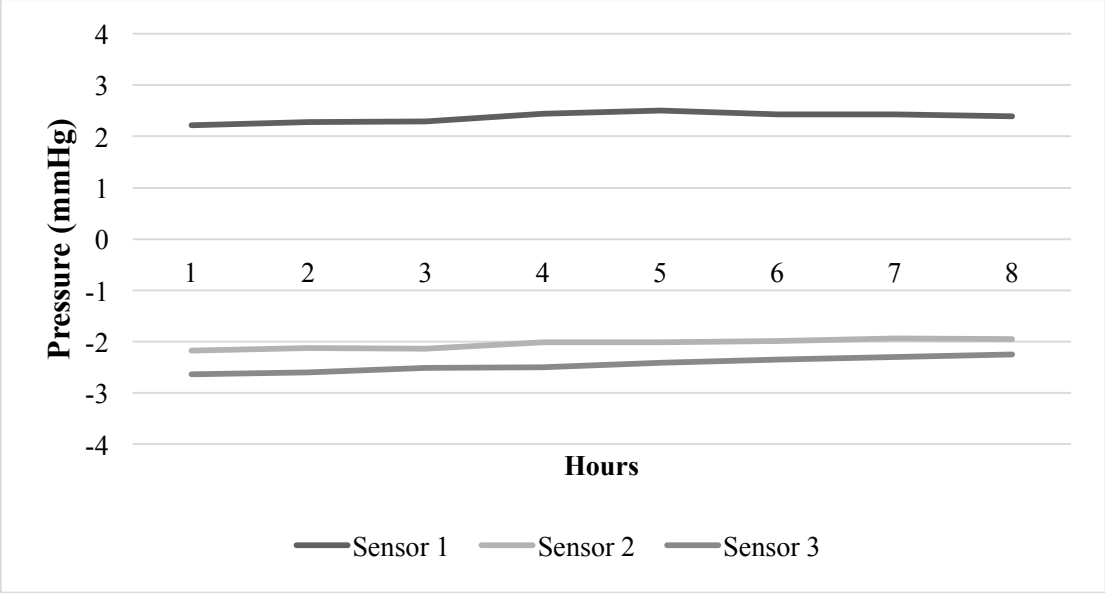


Figure 12.2 The stability of low-resolution manometric measurement is depicted above, with baseline pressure remaining stable throughout recording, within 3 mmHg.

12.3.1 High-resolution Manometry

Pattern of Drift

Two individual components contribute to overall pressure drift, namely a thermal effect and baseline drift. Thermal effect is evidenced by a substantially altered pressure reading at the onset of the study, while baseline drift is noted by an increasing pressure reading with time. Importantly, thermal effect and baseline drift are superimposed on intraluminal pressure, which can only be estimated in-vivo. This contrasts with in-vitro studies that have a known, controllable pressure to which one can directly compare measurement error against. In-vitro, there was evidence of an overall drift in pressure that varied substantially both between studies (15 min studies, $\chi^2(7) = 122.9$, $p < 0.01$; extended duration studies, $\chi^2(5) = 13.4$, $p = 0.02$) and within sensors (ESO catheter, $\chi^2(35) = 75.2$, $p < 0.01$; ESO Z catheter, $\chi^2(35) = 96.8$, $p < 0.01$) over trials.

Thermal Effect

When investigating the thermal effect in further detail, marked variability in both in-vivo and in-vitro recordings was revealed, as detailed in Tables 12.2 and 12.3, respectively. The median across sensors was derived and then analysed for a total study median. Wilcoxon Signed-Rank Test revealed differences in thermal effect between in-vitro and in-vivo studies ($Z = -4.34$, $p < 0.001$). Figure 12.3 depicts the variability across sensors (x-axis) and pressure medians across studies (y-axis) for the in-vivo and in-vitro studies.

Table 12.2 Thermal effect across in-vivo studies using the ESO catheter (mmHg).

		Study 1	**Study 2**	**Study 3**	**Study 4**	**Study 5**	**Study 6**	**Study 7**	**Study 8**
ESO Catheter	*Median*	-4.1	-1.2	-13.3	-12.4	2.5	-11.5	-2.6	-5.7
	(IQR)	(3.9)	(8.4)	(8.6)	(13.5)	(18.1)	(9.7)	(11.0)	(11.3)
	Maximum	8.43	11.9	4.7	6.4	55.3	19.7	104.5	20.1

Table 12.3 Thermal effect across in-vitro studies, using ESO and ESO Z catheters (mmHg).

		Study 1	**Study 2**	**Study 3**	**Study 4**	**Study 5**	**Study 6**
ESO Catheter	*Median*	4.4	-5.3	-0.1	-0.6	-1.7	-2.0
	(IQR)	(3.2)	(10.3)	(6.7)	(5.6)	(1.5)	(1.6)
	Maximum	16.6	11.2	25.9	2.9	-0.3	3.3
ESO Z Catheter	*Median*	3.4	-2.1	-6.0	1.6	2.9	-1.5
	(IQR)	(3.9)	(2.3)	(1.4)	(1.9)	(3.6)	(1.8)
	Maximum	28.3	10.8	-3.1	7.5	11.2	1.3

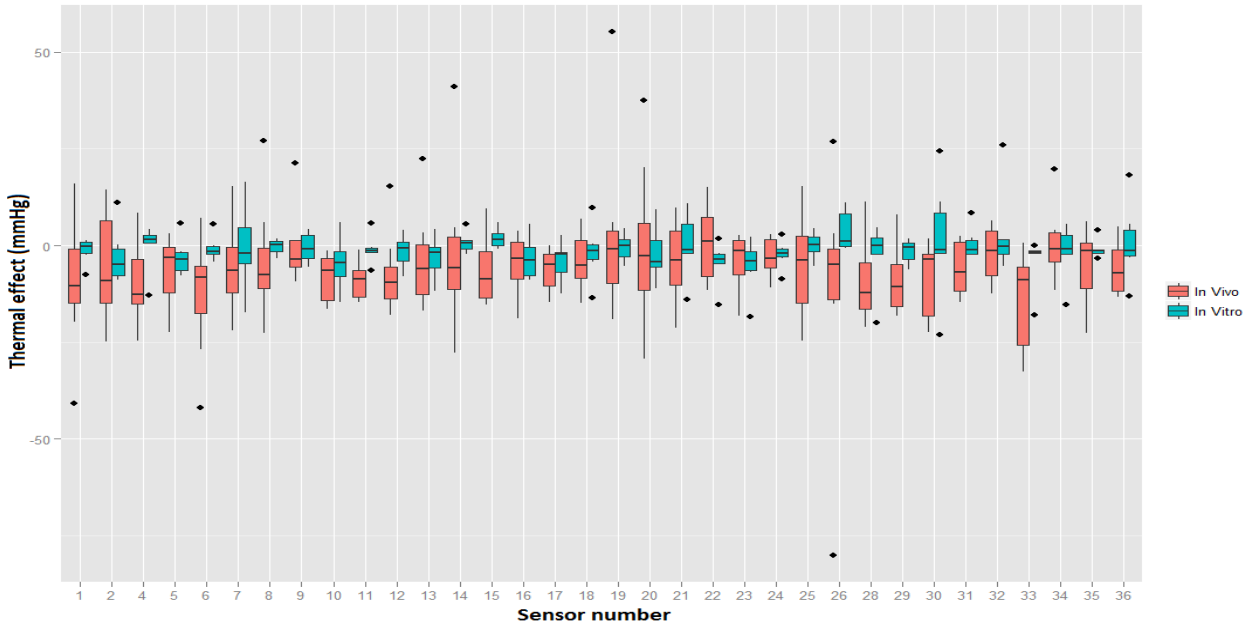


Figure 12.3 The box-plot represents variability of the thermal effect across sensors over in-vivo and in-vitro studies. The line represents the median, the box represents the interquartile range (25th and 75th percentiles) and the whiskers the range.

Baseline Drift

Evaluation of median, maximum and interquartile range of baseline drift per hour across in-vivo and in-vitro studies is summarized in Tables 12.4 and 12.5. A median was taken across sensors and summarized for a total study median. Wilcoxon Signed-Rank Test revealed no significant differences in thermal effect between in-vitro and in-vivo studies (Z = -1.02, p = 0.33).

Table 12.4 Baseline drift across in-vivo studies using the ESO catheter (mmHg/hour).

		Study 1	**Study 2**	**Study 3**	**Study 4**	**Study 5**	**Study 6**	**Study 7**	**Study 8**
ESO Catheter	*Median*	3.0	2.6	2.3	1.7	3.5	2.9	2.8	2.9
	(IQR)	(0.9)	(1.1)	(1.4)	(1.0)	(1.7)	(1.7)	(1.6)	(1.6)
	Maximum	19.2	20.4	21.6	18.7	7.5	9.9	5.4	5.6

Table 12.5 Baseline drift across in-vitro studies, using ESO and ESO Z catheters (mmHg/hour).

		Study 1	Study 2	Study 3	Study 4	Study 5	Study 6
ESO Catheter	*Median*	3.2	3.8	3.1	2.1	2.2	2.0
	(IQR)	(1.3)	(2.2)	(1.1)	(1.1)	(1.1)	(1.2)
	Maximum	6.6*	7.7*	6.5*	5.5	5.5	4.9
ESO Z Catheter	*Median*	3.7	3.1	3.8	4.0	4.0	4.4
	(IQR)	(1.9)	(2.8)	(2.0)	(3.2)	(3.6)	(4.0)
	Maximum	5.9*	6.3*	7.8*	7.5	8.3	9.3

*If sensor 27 is included, the maximum baseline drift for the ESO catheter becomes 55.7, 65.6 and 90.6 across the three studies.

Linearity was calculated in-vitro for each sensor and then averaged across studies in a summary statistic. Baseline drift was found to be linear within a given sensor and trial (R^2 = 0.96). Linearity was similarly high with both the ESO (R^2 = 0.96) and ESO Z catheters (R^2 = 0.93). Similar to the thermal effect, Figure 12.4 depicts the median variability across each sensor (x-axis) and pressure medians across in-vivo and in-vitro studies (y-axis), respectively.

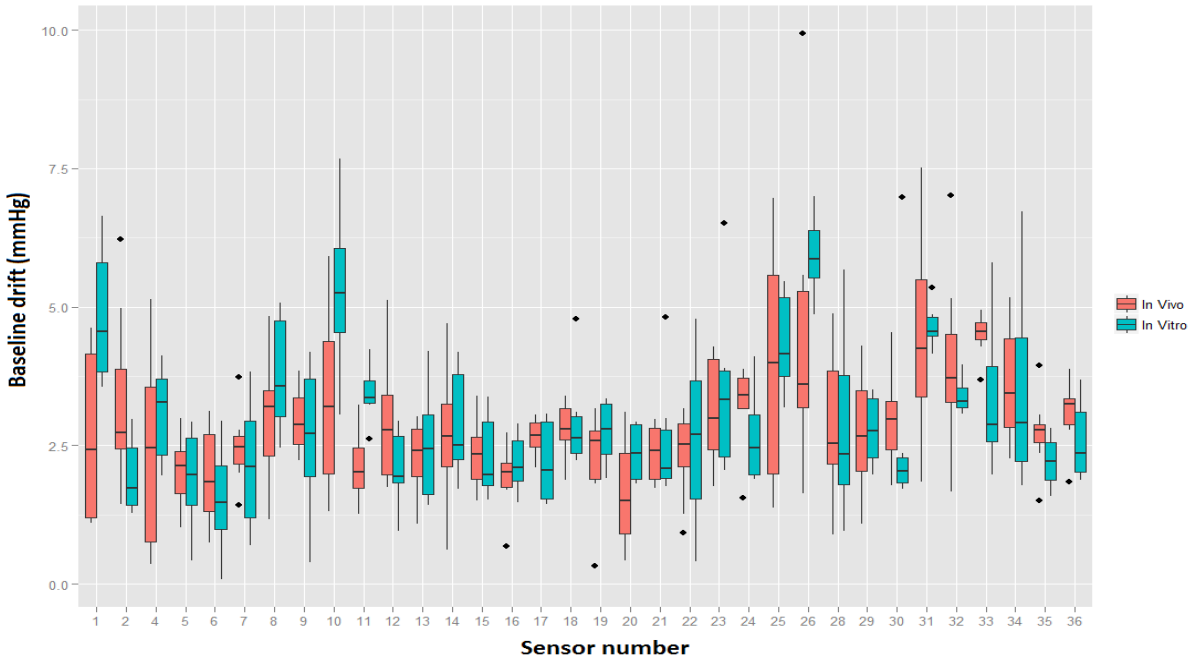


Figure 12.4 The box-plot represents variability of the baseline drift across sensors in the in-vivo and in-vitro studies.

The relative contributions of thermal effect and baseline drift per hour to overall pressure drift for the 5 hr in-vitro studies were investigated. At the beginning of the study, thermal effect contributes to the majority of the overall drift for both the ESO and ESO Z catheters. However, with increasing study duration, baseline drift per hour comprises over 75% of the overall drift by the end of the study due to its linearly increasing property.

Origin of Drift

There was no correlation between thermal effect and baseline drift for the ESO catheter ($r = -0.02$) or ESO Z catheter ($r = 0.13$). The magnitude of the thermal effect and the slope of the linear baseline drift per hour appear to be unpredictable and highly variable.

Replication of the Babaei et al. (2015) analyses were undertaken to investigate the relationship between overall drift and average pressure exposure on a sensor during a recording. Using non-corrected data, a high correlation was found between mean pressure exposure during the 15 min in-vivo study with overall pressure drift ($r = 0.93$, $p < 0.01$) and a moderate relationship between peak pressure exposure during a 15 min study with overall pressure drift ($r = 0.51$, $p < 0.01$). Importantly, when the data were corrected by applying TC, as recommended by the manufacturer, the relationships between overall drift and mean pressure exposure ($r = -0.02$, $p = 0.69$) as well as drift and maximum pressure exposure ($r = -0.05$, $p = 0.39$) disappeared.

A comparison of data with the catheter submerged at two depths was completed to further assess the influence of average pressure exposure and development of overall drift, thermal effects and baseline drift per hour, respectively. Table 12.6 summarizes the median drift (and IQR) across the drifting subcategories for the two depths. The median baseline drift was lower at 4.0 cm depth as compared to 9.0 cm depth, however, there was an increase in median total drift at 4.0 cm depth as compared to 9.0 cm depth. There was no significant difference in median thermal effect.

Table 12.6 Pressure contribution to an overall error across two depths.

	2.9 mmHg (4.0 cm depth)	**6.6 mmHg (9.0 cm depth)**	**Significance**
Median Baseline Drift (mmHg/hour; IQR)	3.7 (0.7)	4.2 (0.6)	$p < 0.01$
Median Thermal Effect (mmHg; IQR)	-0.1 (4.6)	-0.2 (1.0)	$p = 0.65$
Median Total Drift (mmHg/hour; IQR)	20.9 (4.8)	20.7 (4.5)	$p < 0.01$

A Wilcoxon Signed-Rank Test revealed significant differences between the two depths for overall drift ($p < 0.01$) and baseline drift per hour ($p < 0.01$), but no significant differences between the two depths for median thermal effect ($p = 0.65$). The comparisons of thermal effect and baseline drift per hour are represented in Figure 12.5 and 12.6, respectively. The median thermal effect is close to zero due to the frequent occurrence of both negative and positive values across the two depths.

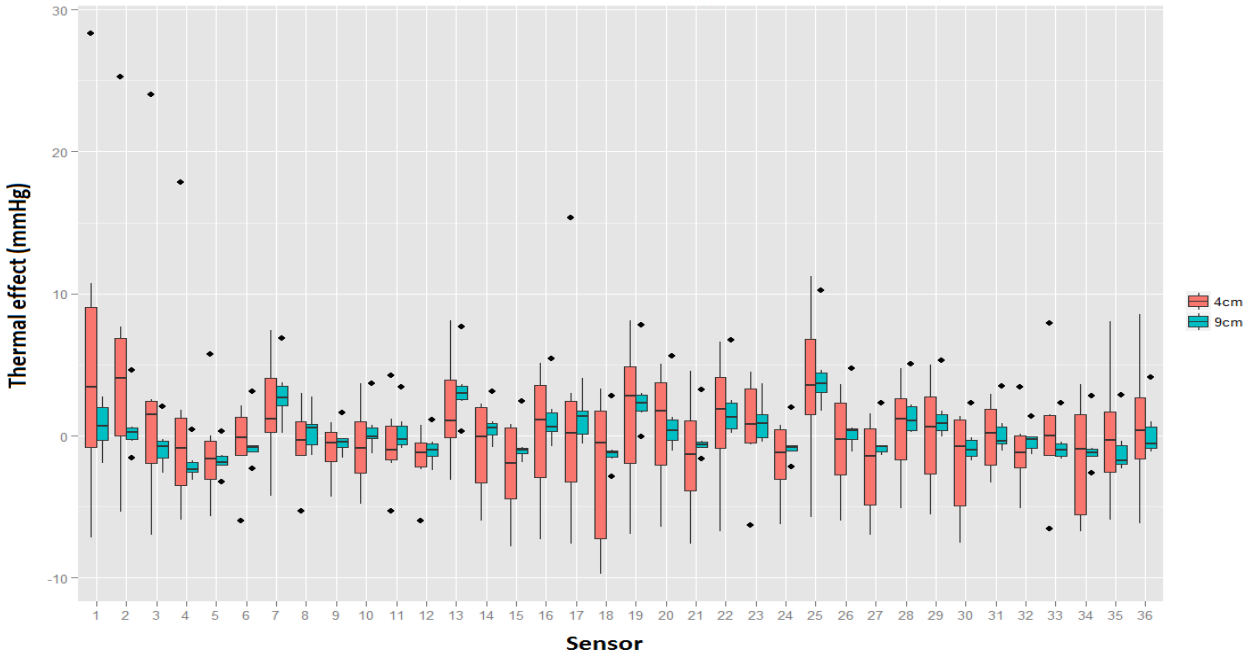


Figure 12.5 The box-plot represents variability of the thermal effect across sensors at two depths.

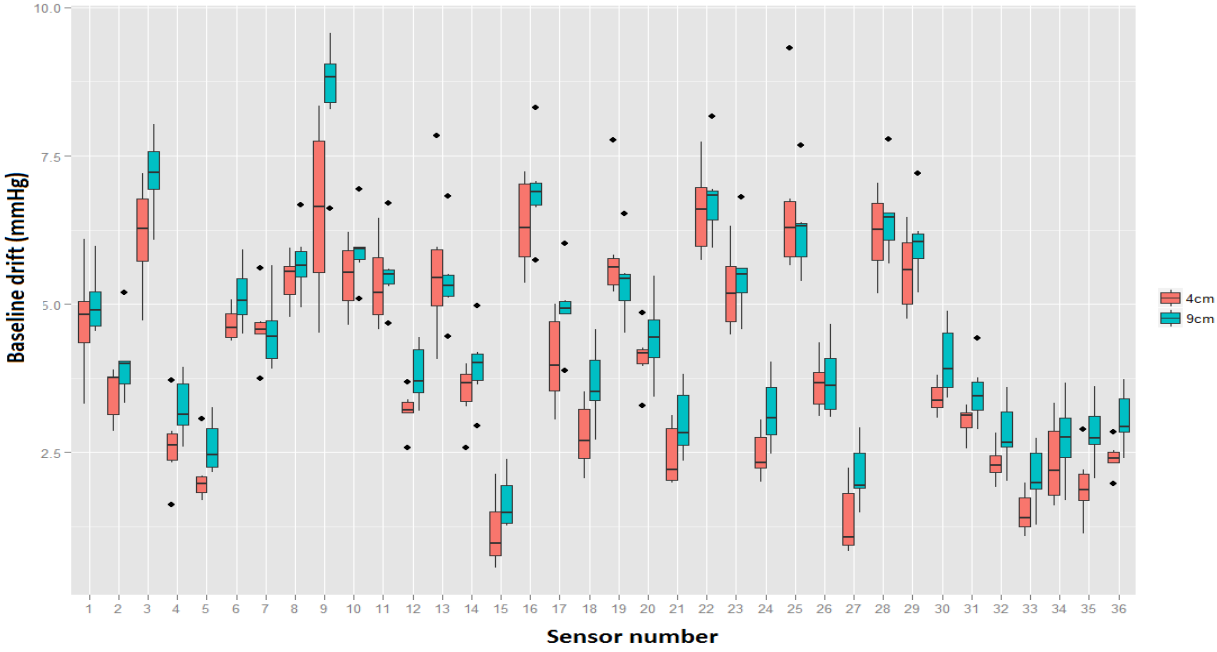


Figure 12.6 The box-plot represents variability of the baseline drift across in two depths.

Correction Methods

For the 15 min in-vitro studies, the median error of the raw data was 3.4 (IQR = 0.77) for the ESO catheter and 3.6 (IQR = 0.47) for the ESO Z catheter. Following correction with TC, the median error reduced to 2.7 (IQR = 0.72) for the ESO catheter and 3.3 (IQR = 0.45) for the ESO Z catheter. ITC was not tested for the 15 min studies as it is intended for extended duration studies. However, both correction methods were analysed in the extended-duration studies; a summary of the median error following correction by TC and ITC is summarized in Table 12.7. In this table, the extended duration studies are segmented into four time periods for evaluation of measurement error over time. As the correction methods were applied to correct substantial drift at the end of extended duration studies, performance of the correction methods at the shorter time points cannot be generalized to shorter duration studies. Short duration studies (<30 min) have substantially less baseline drift and therefore react differently to compensation than the extended duration studies.

Table 12.7 Median error (IQR) across extended duration in-vitro studies evaluating the correction methods as compared to non-corrected data (mmHg).

		Non-Corrected	TC	ITC
ESO Catheter	*30 min*	4.2 (0.9)	14.5 (3.3)	2.3 (2.5)
	2 hr	3.9 (0.8)	13.2 (2.7)	2.5 (3.0)
	4 hr	4.5 (1.8)	11.5 (2.2)	2.4 (3.1)
	End of study	5.2 (2.3)	10.3 (2.0)	2.4 (3.0)
ESO Z Catheter	*30 min*	3.0 (1.4)	17.5 (3.2)	1.8 (0.5)
	2 hr	6.0 (2.5)	13.1 (2.7)	2.6 (0. 2)
	4 hr	9.0 (6.3)	9.6 (3.3)	2.5 (1.0)
	End of study	10.6 (7.0)	9.6 (3.2)	2.2 (1.1)

As seen in Table 12.7, the non-corrected data have increasing median errors over time across studies. This contrasts to the findings of TC, where median error reduces as study duration increases. This is due to the design of TC, as this correction simply shifts the error to the beginning of the study. However, ITC is able to correct the extended duration data with the lowest residual median error due to the two-point correction method. These principles are visually represented in Figure 12.7, a schematic depicting the extended duration correction profiles for TC and ITC from the non-corrected data.

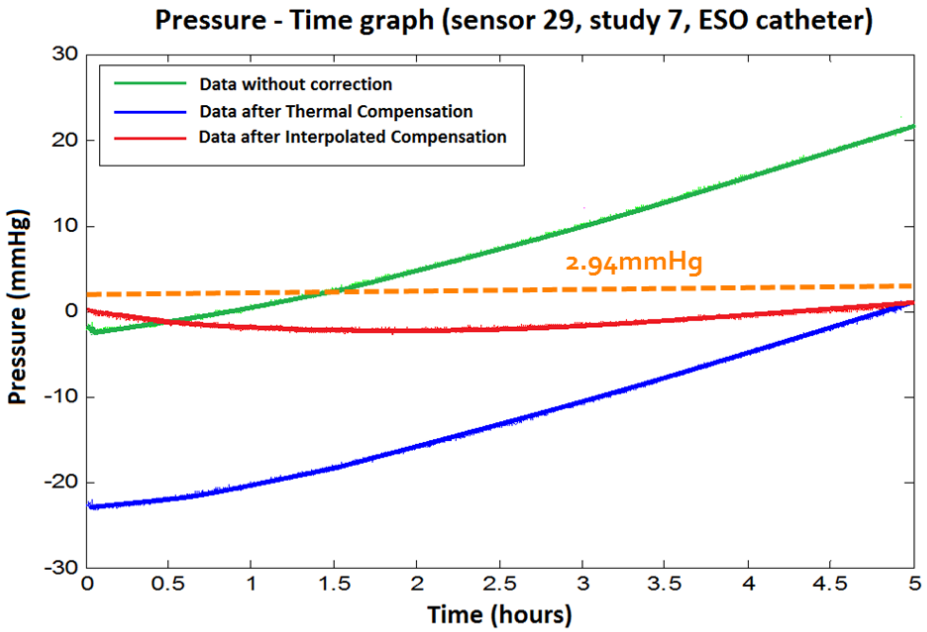


Figure 12.7 Comparison of correction methods using a single example sensor, with pressure-time graph showing non-corrected data, thermal compensated data and interpolated thermal compensated data against the dashed reference line of actual pressure exposure (2.9 mmHg).

Lastly, an analysis was undertaken to investigate accuracy of ITC when no initial TC is applied, as it could be advantageous to perform ITC without the initial 2 min water bath for efficiency and retrospective application of this compensation. As depicted in Figure 12.8 visual analysis of ITC as a single-step compensation (without the initial 2 min water bath) does not correct the thermal effect and inverts the slope of the baseline drift. Both steps of the ITC method are critical for optimized performance of this compensation.

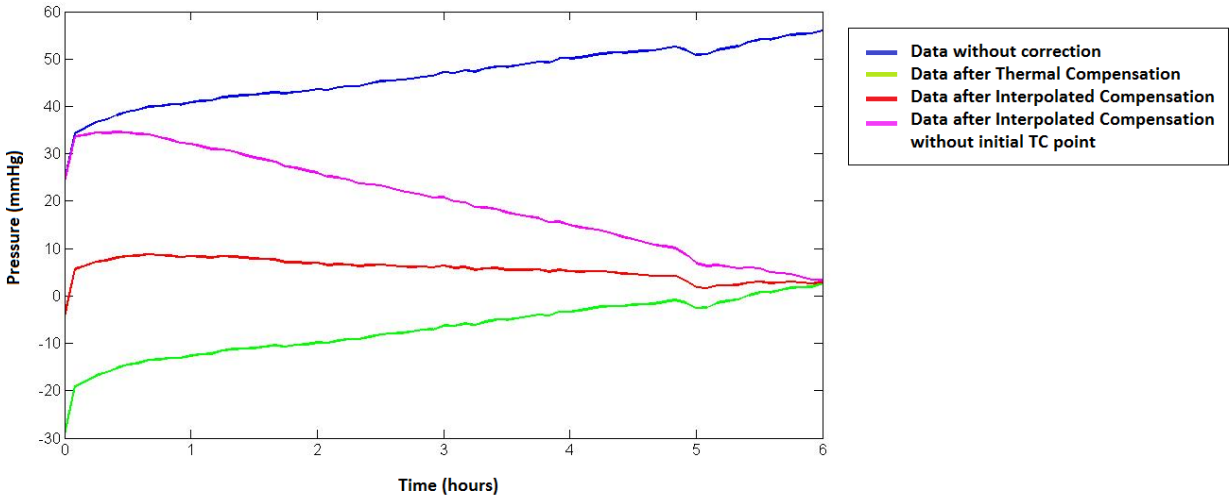


Figure 12.8 Comparison of correction methods including the non-standard use of ITC (pink) without the initial 2 min water bath for efficiency and retrospective application of this compensation.

12.4 Discussion

This study is the first to evaluate pressure drift and correction methods in low- and high-resolution manometry systems in-vitro and in-vivo. Results indicate low-resolution manometry demonstrates highly consistent recording over time. This contrasts to the overall pressure drift in the HRM instrumentation evaluated in the present study, which refutes manufacturer report that pressure uniformity remains within 2 mmHg for 4 hr or less of recording. This overall drift was found to vary significantly between sensors and studies and is not corrected via the standard operating instructions utilizingManoView™ software. Results relating to the HRM drift will be discussed further below.

12.4.1 Pattern of Drift

This study confirms that overall drift is comprised of a thermal effect – a variable reaction secondary to rapid temperature change stabilising after two minutes, and a baseline drift – a linear drift increasing with time (Robertson et al., 2012). This thermal effect and baseline drift per hour are physiologically implausible, as it is unlikely that the human body would have variable and extreme positive and negative pressure readings at intubation, increasing in amplitude throughout the study. Study duration has a direct impact on overall pressure reading due to the constancy of the baseline drift, with pressure readings increasing with time

in all circumstances but with different sensors having different rates of baseline drift per hour. This contrasts with the findings of Babaei et al. (2015), who reported that drift is likely non-linear. In their analyses, they utilize a pharyngeal sensor (e.g., sensor 1) as a baseline measure to track overall pressure drift, arguing this sensor is "recording in a compartment in equilibrium with atmospheric pressure" (p. 297). Although pharyngeal sensors are surrounded by atmospheric pressure at rest, the pharynx is a moving structure that can fluctuate throughout the recording due to extraneous movement associated with breathing and speech. Measurement may also be influenced by catheter positioning (e.g., resting against lateral pharyngeal wall). Due to these constraints, reliance on in-vitro studies, rather than pharyngeal sensors, for confirmation of patterns of drift against a known baseline is critical. Thus, as the pattern of drift consisting of a thermal effect and subsequent baseline drift was easily replicated from previous reports (Robertson et al., 2012) and is evident in-vivo, results support overall drift being comprised of these two interacting elements.

12.4.2 Origin of Drift

With regard to what elements contribute to drift, debate exists as to whether drift results from temperature and duration, or average pressure exposure during a study. As stated previously, Babaei et al. (2015) concluded "pressure drift preferentially affects oesophageal high-pressure zones and strongly correlates with 'average pressure exposure' of a sensor during manometry" (p. 277). They speculated that average pressure exposure on a sensor is the most influential factor contributing to pressure drifts, while other recording parameters, such as duration, only explain a small proportion of overall drift. However, there are notable limitations in their analyses and subsequent conclusions. First, with an average recording duration of 35 min (±14 min), it is unclear if their study durations were sufficient to reveal additional drifting components (e.g., baseline drift). Secondly, if average pressure exposure during a study most accurately predicts pressure drift, it is unclear why sensors evaluated in-vitro would have variable pressure drift. In-vitro, sensors can be placed in a 37°C water bath with constant pressure by keeping sensors at a fixed depth. Thus, all sensors in-vitro were exposed to the same average pressure. Therefore, variable pressure drift, despite equal average pressure exposure, directly negates the possibility of average pressure exposure being the principal determinant of pressure drift. Lastly, the authors do not report whether they performed TC prior to calculating average pressure exposure to a sensor. If compensation is not applied, then average pressure exposure to a sensor would be calculated including

pressure drift, artificially inflating the average pressure exposure for sensors that coincidentally had higher rates of pressure drift.

This study support this notion. Although a significant correlation was found between pressure drift and non-corrected data, once the data were corrected based on manufacturer recommendations, relationships between pressure drift and average pressure exposure ($r = -0.02$) and between pressure drift and maximum pressure exposure ($r = -0.05$) disappeared. The high correlation reported by Babaei et al. (2015), replicated above without correction, is likely due to correlating pressure readings that were non-corrected (e.g., still containing drift inherent in the reading) with the drift itself. It is clear that average pressure exposure is not a primary mediator of pressure drift when the data is corrected based on manufacturer recommendations. Nevertheless, when comparing data derived from the two depths, significant differences were found in baseline drift per hour and overall pressure drift for extended duration studies. Increased pressure may modulate the gradient (e.g., slope) of the baseline drift per hour but further investigation is needed to explore this possibility. Due to the highly variable nature of the data with an inclination toward significant outliers, it is important to balance these significant findings by comparing medians and inter-quartile ranges, which are closely overlapped and the non-significant difference of thermal effect between the two depths. These results support the substantial role of temperature and duration in modulating overall pressure drift, replicated from previous reports (Robertson et al., 2012) and evidenced in-vivo.

12.4.3 Correction Methods

With regard to correction methods, this is the first study to trial available correction methods via standard operating instructions employing ManoView™ software. Previous studies evaluated the theory of the TC and ITC correction methods using self-generated software. However, the applicability and generalisability of these custom programs are not known and direct testing of the system-based correction methods is necessary.

Our findings support previous research that documents the standard TC process does not correct the error associated with the drift, but simply reallocates the error to the beginning of the study (Robertson et al., 2012). In shorter duration studies, the median error associated with correcting the drift with TC was greater than manufacturer statements that pressure

uniformity remains within 2 mmHg for 4 hours or less of recording. For extended duration studies, TC performs even more poorly, with median errors greater than 7.4 mmHg.

In contrast, ITC, with its two-step linear interpolation correction method, is able to correct the error associated with baseline drift, even in extended duration studies. However, the user must be aware of this option to pursue its activation in the software, as ITC is not reported in the ManoScan™ or ManoView™ user manuals. Once requested by name, the manufacturer must intervene to enable this software option. Nevertheless, ITC was found to be the most effective correction method with corrected values having an error roughly within the stated pressure uniformity measure of 2 mmHg. Although this method is superior, it is more time-consuming, requiring the user to record a 2 min water bath at 37°C prior to recording the study. Further, since this 2 min water bath is required in order to apply ITC appropriately, previously collected data cannot be retrospectively corrected using ITC by the software (Figure 12.7).

12.4.4 Limitations

Further work is needed to determine the electromechanical mechanisms of HRM sensors which lead to pressure drift. Previous publications have speculated that the catheter design may lend itself to deformation due to an air gap within the sensing membrane from a rigid surface of a metallic inner electrode (Babaei et al., 2012). With different metals in use, such as copper, the variable distortions following temperature shock at intubation may play a critical role in generating pressure drift. Although analog signals often have some level of baseline drift, how or why this baseline drift is variable across studies and between sensors is not known. Further investigation by the manufacturer is needed to understand the development of drift as a result of the intrinsic nature of the catheter. The current study investigates pressure drift in two discrete catheters. As there is notable variability both between sensors and across catheters, ongoing research investigating a greater number of catheters is warranted. Additionally, it is unclear how additional compensations, such as the weekly ManoScan™ in-vivo compensation are interacting with pressure drift and the related compensation methods.

Chapter 13: The Effect of Topical Nasal Anaesthetic (TNA) on Tolerability and Pharyngeal Pressure in Healthy Adults: A Double-Blind Study

13.1 Introduction

TNA is commonly used in research and clinical examination to improve patient comfort and ease of catheter placement during manometry. However, it is unknown if desensitizing the nasal mucosa affects sensorimotor aspects of swallowing. This is critical as the majority of studies investigating pharyngeal swallowing with HRM utilize TNA prior to catheter insertion (Hammer et al., 2009; Hoffman et al., 2012; Jones, Hammer, et al., 2014; McCulloch, 2010; Mielens et al., 2012; O'Rourke et al., 2014). The most commonly provided TNA is a 2% viscous lidocaine hydrochloride solution. Some studies administer a secondary anaesthetic, sprayed or gargled intra-orally (Hoffman et al., 2012, 2010; McCulloch, 2010; O'Rourke et al., 2014), or directly lubricate the catheter with viscous lidocaine in addition to the lubrication methods applied above (Hoffman et al., 2012).

There is a discrepancy in the literature whether TNA improves perception of comfort of this and similar exams (Bonaparte, Javidnia, & Kilty, 2011; Carmona-Sánchez, Valerio-Ureña, & Valdovinos-Díaz; Fife et al., 2015; Gaviola, Chen, & Chia, 2013; Lester et al., 2013; Sunkaraneni & Jones, 2011). Published protocols for implementation of pharyngeal HRM in clinical practice recommend routine application of TNA despite a lack of evidence regarding effects on pharyngeal swallowing (Knigge et al., 2014). As TNA carries the risk of impairing sensory aspects of pharyngeal swallowing (Fraser et al., 2003), clear benefits should be determined prior to routine application of numbing agents when evaluation oropharyngeal swallowing.

Previous studies have investigated the use of TNA in regard to oesophageal manometry (Nasrallah & Hendrix, 1987) and with similar instrumental techniques, such as FEES (Bonaparte et al., 2011; Fife et al., 2015; Kamarunas, McCullough, Guidry, Mennemeier, & Schluterman, 2013; Lester et al., 2013; O'Dea et al., 2015). Evidence regarding efficacy and contraindications for use of TNA with trans-nasal intraluminal devices have conflicting results. A recent Cochrane review investigated eight randomized control trials in a review of TNA use with FEES (Sunkaraneni & Jones, 2011). Results from five of the eight studies revealed no improvement in procedure comfort and further demonstrated negative effects

such as unpleasant taste and increased associated cost (Sunkaraneni & Jones, 2011). This contrasts to a double-blind, placebo-controlled randomized trial by Bonaparte et al. (2011), evaluating procedure tolerance of FEES. They used a lidocaine spray, without lubrication, in 22 patients requiring examination. Results indicated a significant reduction ($p < 0.01$) in discomfort with TNA compared with plain lubricant (Bonaparte et al., 2011). Kamarunas et al. (2013) also evaluated swallowing function and procedure comfort in healthy participants ($n = 36$). Participants were provided with 0.4 ml of 2% viscous lidocaine hydrochloride or the same quantity of lubricant prior to intubation with FEES. Similar to the Cochrane review, results indicate no difference in participant report of comfort or laryngopharyngeal sensory thresholds (Kamarunas et al., 2013). However, they acknowledged that TNA may have subtle effects on swallowing function, with a faster stage transition for a 10 mL liquid bolus during the TNA condition (Kamarunas et al., 2013).

Results from more recent studies expand on the Kamarunas et al. (2013) study by providing further evidence regarding alterations to swallowing function subsequent to provision of TNA. Lester et al. (2013) evaluated healthy participants ($n = 20$) with FEES using 1 mL of 4% lidocaine during two evaluation sessions, randomized (but not blinded) to receive TNA or non-anaesthetized evaluation. While TNA was found to improve procedure comfort significantly ($p < 0.05$), the results reveal a significant reduction in swallowing function ($p = 0.001$) as evidenced by a poorer Penetration-Aspiration scale score (> 4) in the TNA condition. A similar study by Fife et al. (2015) evaluated comfort and presence of aspiration during FEES in dysphagic patients ($n = 24$). Participants received two evaluations in one day, with application of 0.5 mL of 4% lidocaine solution immediately following the non-anaesthetized evaluation (Fife et al., 2015). Although participants were not blinded and a placebo was not utilized, their results revealed significantly less discomfort during the examination in the TNA condition as compared to the lubricant condition (Fife et al., 2015). Importantly, the results indicated a 33% increase in aspiration rating in the TNA condition; however, there were no other significant impairments in swallowing function ($p = 0.65$; Fife et al., 2015). The findings above contrast to a study evaluating tolerability and swallowing function in dysphagic patients ($n = 17$) with 0.2 mL of 4% lidocaine in an ‘abbreviated FEES study’ (O’Dea et al., 2015). Results indicated improved tolerability in the TNA condition with no impairment in swallowing function but this may be due to fewer bolus trials and sizes

in the 'abbreviated study' than comparable research (Fife et al., 2015; O'Dea et al., 2015). As is evident, the current literature is mixed with regard to benefits and contraindications of use of TNA.

This lack of consensus is compounded by an absence of data regarding effects of TNA in reference to pharyngeal HRM. Therefore, the present study evaluated the impact of TNA on participant perception of procedure comfort, as well as timing and amplitude of pharyngeal swallowing using pharyngeal HRM. It was hypothesized that there would be no significant differences in the participant report of procedure discomfort between the two TNA and placebo test conditions. Further, it was hypothesized that healthy participants would demonstrate no difference in amplitude and timing of pharyngeal pressure under the TNA and placebo conditions. Results from this study may allow refinement of published protocols for conducting this examination and offer further information to guide best practice of pharyngeal HRM and similar trans-nasal intubation techniques.

13.2 Materials and Methods

13.2.1 Participants

Twenty healthy participants (3 males, 17 females), ranging in age 20–52 years (mean = 27 years), participated in the study. No participant reported a history of dysphagia, neurological or muscular impairment, or use of any medications that are known to affect swallowing. All participants denied receiving any prior trans-nasal intubation. Ethical approval was obtained from the local institutional review board and informed consent was obtained from all participants prior to commencement of data collection.

13.2.2 Equipment

HRM studies were completed using the ManoScan 360™ High-resolution Manometry system (Model A120) with a 2.75-mm diameter ManoScan™ ESO catheter (EPS0042). In-vivo calibrations were routinely performed and each recording session was preceded by calibration per standard operating instructions. All studies were corrected for thermal effect measurement error with application of a standard 'Thermal Compensation' correction method, as described in Chapter 11.

13.2.3 Procedures

Participants were seen for two sessions. The TNA was prepared, handled and applied by a licensed dental surgeon. The participant and the investigator responsible for catheter insertion were blinded to the use of lubricant (placebo) or TNA. Both were clear gels with no features (e.g., colour or odour) that could have informed the participant or primary investigator responsible for catheter insertion as to the condition being applied. In the experimental condition, 0.4 ml of 2% viscous lidocaine hydrochloride was applied to one side of the nasal cavity via a cotton-tip applicator. In the sham condition, 0.4 ml of lubricant was similarly applied. The cotton-tip applicator remained in the nares for 2 min in both conditions. The selected naris of entry, based on participant preference, was used in both sessions. The order of the experimental (TNA) and placebo (lubricant) conditions between session one and session two was counter-balanced, with half receiving anaesthetic in the first session and the other half receiving anaesthetic in the second session.

The manometric catheter was placed transnasally using the routine protocol described in Chapter 9 and was taped securely to the external nose with medical adhesive tape. The catheter was inserted until sensor 1 was located just inside the naris with sensor 36 in the cervical oesophagus, enabling the length of the upper aerodigestive tract to be evaluated in its entirety. For both sessions, each subject was asked to perform five dry swallows at a self-generated pace, approximately one swallow every minute to record baseline function. Sips of water were offered as needed to moisten the mouth throughout. Following this, the participants ingested five 10-mL water swallows at a self-generated pace. On completion of the swallowing tasks, the participant completed a 100-mm visual analog scale, rating the procedure from ‘0’ (no discomfort) to ‘100’ (extreme discomfort). A horizontal, continuous 100 mm visual analog scale was utilized due to its simplicity in participant rating, reliability reported in the literature and sensitivity to change in pain ratings as compared to other pain rating scales (e.g., 4-point rating scale; Alheid, Milsom, & McCrimmon, 2004; Bourdel et al., 2015; Breivik, Björnsson, & Skovlund, 2000; Johnson, 2005; Peters, Patijn, & Lamé, 2007; Skovlund, Bretthauer, Grotmol, Larsen, & Hoff, 2005; Williamson & Hoggart, 2005). The catheter was then removed from the nasopharynx and the session was completed. Participants returned for the second evaluation within 1–5 days following the first session, receiving the opposing TNA or placebo condition. The evaluation protocol and swallowing tasks were replicated, as specified above.

13.2.4 Data Analysis

A clinical researcher and primary investigator rated visual analog scale scores; inter-rater reliability was computed with Pearsons product-moment correlation coefficient. Pharyngeal pressure data from HRM were corrected with the standard TC process and exported for post-hoc analysis with external software (MATLAB R2014a, The MathWorks Inc., Natick, MA, 2014). Since the primary investigator was blinded to study condition, they performed the analysis. Of the 36 measurement sensors, the sensors in the pharyngeal region were extracted for analysis. A pharyngeal range was selected by identifying the sensors immediately below the velopharyngeal region (Knigge et al., 2014) and immediately above the most superior characteristic 'M-wave' pattern representative of the UES region (Chapter 8). The maximum pharyngeal pressures across the five swallows in each condition, namely dry and 10 mL liquid swallows, were extracted. These maximum values were averaged for each participant and each two swallowing conditions, dry and 10 mL swallows, respectively. From this average, the mean pharyngeal pressure was reported. The slope of the pressure was used to investigate temporal characteristics of pharyngeal swallowing. A slope was calculated for both dry and liquid swallows, respectively. In each condition, a best fit line was created from the maximum peak of each pharyngeal sensor for each participant. Similar to measuring peak-to-peak latency in low-resolution manometry, as discussed in Chapter 7 and 8, the slope allows measurement of peak-to-peak latency across a greater number of sensors, reducing the potential for poor inter-rater reliability inherent in individual sensor selection in measurement of HRM, as discussed in Chapter 12. Comparisons were made for both dry and liquid swallows using paired-sample t-tests investigating condition effects (placebo versus TNA) and trial effects (session 1 versus session 2). Parametric statistics were used as difference scores for the condition effects were normally distributed, as assessed by Shapiro-Wilk's test ($p = 0.99$). Statistical analyses were completed with SPSS statistical software.

13.3 Results

13.3.1 Perceptual ratings

All participants tolerated the procedures and completed the study protocol (n = 20). They completed the second procedure on average 2.0 days following the first (SD = 1.4 days). The measurement of the visual analog scale scores were highly reliable between two raters (r = 0.98). A box-plot displaying visual analog scale ratings are depicted in Figure 13.1; higher ratings indicate increased procedure discomfort. Regarding condition effects, visual analog

scale ratings for procedure tolerability were similar under lubricant (38.38 ± 19.92) and TNA conditions (33.78 ± 18.91), with no detected significant differences [t(19) = 1.23, p = 0.23]. Additionally, there were no trial effects, with no difference [t(19) = 1.38, p = 0.18] in discomfort at the second evaluation (33.53 ± 22.60) as compared to the first evaluation (38.63 ± 15.54).

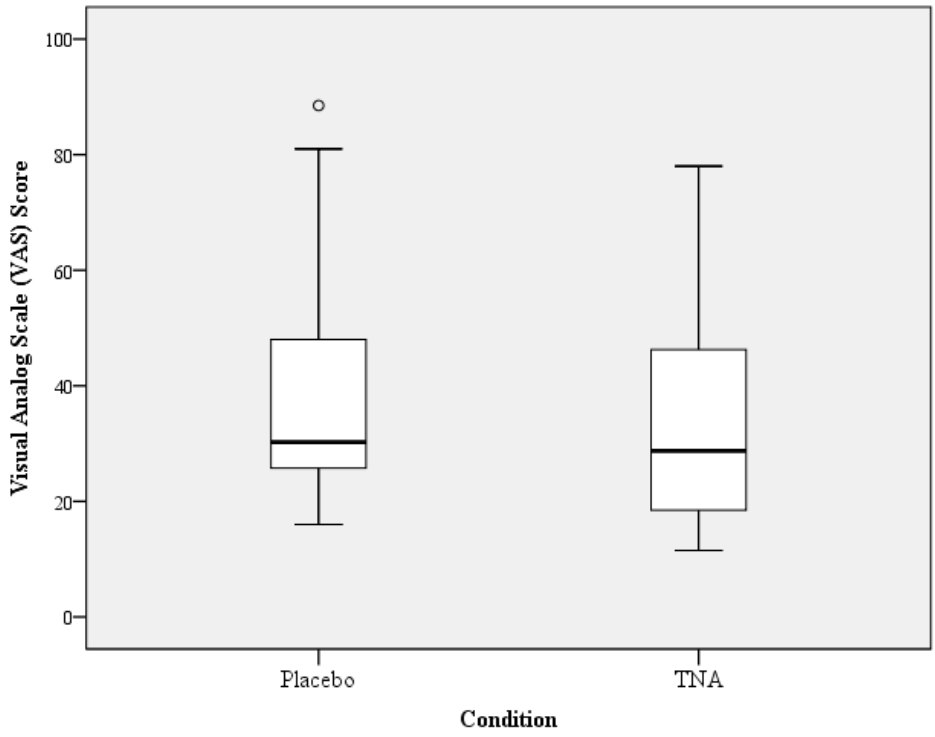


Figure 13.1 Box-plot comparing self-perceived procedure comfort across participants (n = 20) in the TNA and placebo (lubricant) conditions. The median is represented by the horizontal line, with the box representing the inter-quartile range. The minimum and maximum values are represented by the whiskers, including the single outlier denoted in the placebo condition.

13.3.2 Pharyngeal Pressure

Slope and amplitude of pharyngeal pressure were compared between anaesthetic and placebo conditions for dry (saliva) and 10-mL liquid swallows, respectively, as specified in Table 13.1. There was a significant difference in condition effects between mean pharyngeal pressure [t(19) = 2.51, p = 0.02] during dry swallowing, with higher average pressure in placebo conditions. This contrasts to a lower maximum pressure [t(19) = 2.88, p = 0.01] during dry swallowing in placebo conditions. There were no differences in average and

maximum pressures during10-mL liquid swallowing. While there was no difference in the slope of the pressure in dry swallowing, there was a difference [t(19) = -2.93, p = 0.01] in the slope of 10-mL liquid swallows.

Table 13.1 Differences in slope and amplitude (mmHg) of pharyngeal pressure as a result of condition effects (e.g., anaesthetic and lubricant conditions).

	Dry Swallows			**Liquid Swallows (10 mL)**		
	TNA (SD)	Placebo (SD)	Sig. ($p < 0.05$)	TNA (SD)	Placebo (SD)	Sig. ($p < 0.05$)
Average Pressure	102.24 (21.16)	108.92 (18.24)	0.02*	96.42 (21.93)	96.69 (23.80)	0.93
Maximum Pressure	160.01 (29.56)	146.59 (29.56)	0.01*	143.59 (36.77)	145. 35 (28.88)	0.73
Slope	0.11 (0.04)	0.12 (0.04)	0.16	0.11 (0.04)	0.14 (0.04)	0.01*

Relevant to trial effects, there were no significant differences detected between the first and second evaluation sessions for mean amplitude [dry swallowing, t(19) = -0.80, p = 0.43; liquid swallowing, t(19) = 2.07, p = 0.06] and maximum amplitude of pharyngeal pressure [dry swallowing, t(19) = -0.99, p = 0.39; liquid swallowing, t(19) = -1.46, p = 0.14]. While there were no significant trial effect differences in slope for dry swallows between the first and second sessions [t(19) = -1.46, p = 0.16], there was a difference in slope [t(19) = -2.93, p = 0.01] for 10-mL liquid swallows between sessions.

13.4 Discussion

This double-blind study is the first to have investigated effects of TNA on tolerability and pharyngeal pressure using HRM. Results indicate TNA provides no improvement in procedure comfort, consistent with previous publications using FEES (Kamarunas et al., 2013; Sunkaraneni & Jones, 2011). However, TNA and placebo conditions both had marked inter-subject variability in comfort ratings, as demonstrated by a large standard deviation around the mean. Variability in the VAS discomfort ratings are comparable to previous publications using similar methodology. Bonaparte et al. (2011) used a 100 mm VAS in a double-blind, randomized control study investigating FEES, with 100 indicating extreme discomfort, similar to the present study. While they had a lower VAS scores following

provision of three larger 10 mg doses of lidocaine hydrochloride spray, their control scores of 35.6 (SD = 25.8) are comparable to the ratings in the present study. As seen in the abovementioned results, the range of comfort ratings between 9.8–61.4 highlights the substantial variation between participants in tolerability of nasal intubation procedures in the present study. This illustrates the importance of dose and methodology in studies of TNA. For example, many of the studies that found an effect of TNA in improving procedure comfort did not implement blinding (Lester et al., 2013), use of placebo (Fife et al., 2015) or randomization in the order of provision of TNA and placebo (O'Dea et al., 2015). This has the potential to greatly bias results.

There was a reduced average pressure, with a wider range of pressure during dry swallowing. This is coupled with an increased maximum pressure, highlighting increased variability of amplitude in dry swallows under TNA. The similar amplitude across TNA and placebo liquid swallows could reflect the reduced pressure needed for in ingestion of thin liquid boluses, aided by gravity. Interestingly, the slope in the TNA liquid swallowing was less steep, denoting an increased duration of the pharyngeal swallow. Importantly, however, the slope of the liquid swallowing was also significantly different between the first and second sessions, which may reflect variability in this measure regardless of TNA use. As this study did not include instrumentation to investigate bolus flow, subtle differences in liquid swallowing, such as increased penetration in healthy participants (Lester et al., 2014), could have been overlooked.

The present study is not without limitations. As noted above, inclusion of supplementary instrumental techniques to enable analysis of swallowing biomechanics and bolus flow, such as VFSS, would aid in more comprehensively evaluating changes to swallowing function after TNA. Further, a sample which is both larger and includes patients with dysphagia is warranted, as studies differ in effect of TNA between healthy participants and patients with dysphagia, who may be more sensitive to subtle changes resulting from anaesthetic (Lester et al., 2013; O'Dea et al., 2015). Further research is also warranted using larger diameter HRM catheters, which may lead to greater discomfort in non-anaesthetized conditions. Research with larger diameter catheters report use of additional oral (gargled) applications of anaesthetic (Hoffman et al., 2012, 2010; McCulloch, 2010; O'Rourke et al., 2014), which may affect oropharyngeal swallowing to a greater degree. Nevertheless, limited improvement

in comfort and possible impact on pharyngeal swallowing supports the recommendation that TNA is likely not necessary prior to intubation with a 2.75-mm HRM catheter. This affects current published protocols for clinical evaluation with HRM (Knigge et al., 2014) and further research is needed to update recommendations for best practice using pharyngeal HRM.

Chapter 14: Reliability of Clinical Analyses of Swallowing using Pharyngeal High-resolution Manometry

14.1 Introduction

Similar to low-resolution manometry, HRM was initially designed and optimized for evaluation of oesophageal function. Research over the past decade has led to integrative software platforms that not only display intraluminal pressure in topographical plots, but use algorithm-based classification systems to aid interpretation of oesophageal HRM pressure profiles (Fox & Bredenoord, 2008; Hernandez, Ratuapli, Burdick, Dibaise, & Crowell, 2012; Kahrilas & Sifrim, 2008; Pandolfino et al., 2009; Singendonk et al., 2015). This work has been supported by evaluation of reproducibility (Bogte, Bredenoord, Oors, Siersema, & Smout, 2011), inter-rater and intra-rater agreement (Hernandez et al., 2012; Tae Hee Lee et al., 2014; Singendonk et al., 2015), evaluation of body position effects (Ciriza-de-Los-Ríos et al., 2015) and development of normative datasets relevant to the oesophagus (Bogte, Bredenoord, Oors, Siersema, & Smout, 2013).

Application of this technology to oropharyngeal swallowing has been widespread in recent years (Geng, Hoffman, Jones, McCulloch, & Jiang, 2013; Hoffman et al., 2012, 2013, 2010; Jones, Hoffman, et al., 2014; Lin et al., 2014; McCulloch, 2010; Salvador et al., 2009; Takasaki et al., 2008, 2011). However, there are currently no commercially integrated platforms available for the ManoScan^{TM} system to analyse pharyngeal swallowing, with the exception of the UES (Lee et al., 2014). Although ongoing work is exploring classification models of pharyngeal swallowing similar to those used in oesophageal analysis (Mielens et al., 2011), there is no clear consensus on optimal measurements of pharyngeal swallowing with HRM. Most publications rely on software such as MATLAB to analyse pharyngeal swallowing outside of commercial HRM devices (Hammer et al., 2009; Hoffman et al., 2012, 2010; Jones, Hammer, et al., 2014; Ryu et al., 2015) and reliability of pharyngeal HRM is limited to a study by Jones et al. (2016) which investigated a custom MATLAB programme. They evaluated the reliability of a custom-built software programme after provision of a 20-min training session to 20 raters with varying experience (e.g., expert and novice speech-language pathologists). Raters analysed 30 HRM plots. Results indicated that the external analysis program performed with fair-to-high inter-rater reliability (ICC = 0.54-0.99) and intra-rater reliability (ICC = 0.67-1.00) across all experience levels. Although these findings

are promising for future development of automated analysis programmes, clinical users of pharyngeal HRM are unable to access these custom technologies and are currently reliant on evaluation of swallowing with system-based technologies.

In a thorough and practical review, Knigge et al. (2014) provided the only published clinical protocol for analysis of HRM spatiotemporal plots using existing system-based technologies (e.g., ManoScan™ HRM systems). Knigge et al. (2014) recommend evaluation of pressure and temporal characteristics of three anatomical regions during swallowing. These measures include "duration(s) of swallow and UES opening; mean maximum closure and bolus clearance pressures (mmHg) at the velopharynx, tongue base region and UES; and mean minimum pressure (mmHg) during UES opening" (p.5). These measurements and anatomic definitions have been used in previous publications (Hoffman et al., 2010; Lin et al., 2014b; McCulloch, 2010; Takasaki et al., 2011) and this framework appears to have been adapted in automated analysis programs described in the literature (Jones, Hoffman, et al., 2014). The reliability of this technique is unknown. Therefore, the aim of the current study was to evaluate the reliability of clinical swallowing measurements made using the analysis method described by Knigge et al. (2014) – a critical to guide current clinical users of pharyngeal HRM to further understand best practice regarding this technique.

14.2 Materials and Methods

14.3.1 Participants

Five clinical researchers participated in this study. All raters were speech-language pathologists with a specialty in dysphagia, with an average of 5.3 yr experience (range = 4–7 yr). Four raters reported use of pharyngeal manometry in clinical practice, with expertise self-rated as two skilled, two moderate and one novice.

14.3.2 Equipment

High-resolution manometry studies were completed using the ManoScan 360™ HRM system (Model A120). In-vivo calibrations were routinely performed and each recording session was preceded by calibration according to standard operating instructions. All studies were corrected for thermal effect measurement error with application of the standard TC method, as recommended in the User Guide. The primary investigator performed all HRM

evaluations, with catheter insertion performed according to a standard protocol (Knigge et al., 2014).

The ManoView™ system-based analysis software, utilizes a Smart Mouse™ feature to acquire quantitative measurement information by using right and left clicks. There are two visualization modes on the ManoView™ system-based analysis software. The first is the contour mode, which shows the swallowing pressures as a spatiotemporal plot, with pressure encoded as colour. The second mode is the line trace mode, which depicts swallowing-related pressure as simple line traces, similar to traces provided by low-resolution manometric systems. The Smart Mouse™ tool has different functions when used for analysis of the spatiotemporal plot (the contour mode) as compared to analysis of the waveform data (the line trace mode). In contour mode, the Smart Mouse™ can be used by dragging the mouse to highlight a rectangular area of interest. Within this area, the feature will display pressure characteristics including minimum, maximum and average pressure, as well as additional measures such as velocity. On the line trace mode, the Smart Mouse™ tool enables analysis of time between two points, such as onset and offset of pressure.

Swallows were selected at random from a database of patients and healthy participants from the Rose Centre for Stroke Recovery and Research. To be included in the database, patients and healthy volunteers provided written consent for possible inclusion of their data in future analyses. Three individual swallows were selected from three healthy participants and three patients with dysphagia, respectively. One swallow from each subject was randomly selected and repeated for evaluation of intra-rater reliability. All selected samples were saliva swallows to reduce confounding effects of variable bolus size or type.

14.3.3 Procedures

All raters underwent a 20-min training session to learn analysis of the ManoScan 360™ HRM spatiotemporal plots. The training consisted of independent reading of the Knigge et al. (2014), with subsequent verbal discussion of the definitions provided in the text, as shown in Figure 14.1. Anatomic definitions were critical for appropriate landmark identification for durational and amplitude measures. As specified in the text, the velopharyngeal region was defined as “at least two channels at the superior aspect of the pharyngeal spatiotemporal plot”, while the tongue base was the region immediately inferior to the velopharyngeal

channels (Knigge et al., 2014; p. 5). Three measurements were made relating to UES function: UES resting pressure, UES nadir pressure and UES maximal post-swallowing pressure. UES resting pressure was identified as "the band of pressure spanning between swallowing efforts" while "UES superior excursion and the channel for measurement of minimum pressures during UES opening" could be identified by reduction in pressure secondary to UES opening immediately followed by the post-swallow pressure (Knigge et al., 2014; p. 5). Verbal description of the annotated image depicted in Figure 14.1 was provided. Raters were as well provided this image on a fact sheet as reference throughout the rating session, a technique reported in previous HRM reliability methodology (Singendonk et al., 2015). Raters independently analysed the 24 swallows at a self-generated pace. All swallows were coded for blinding and randomized within and across raters.

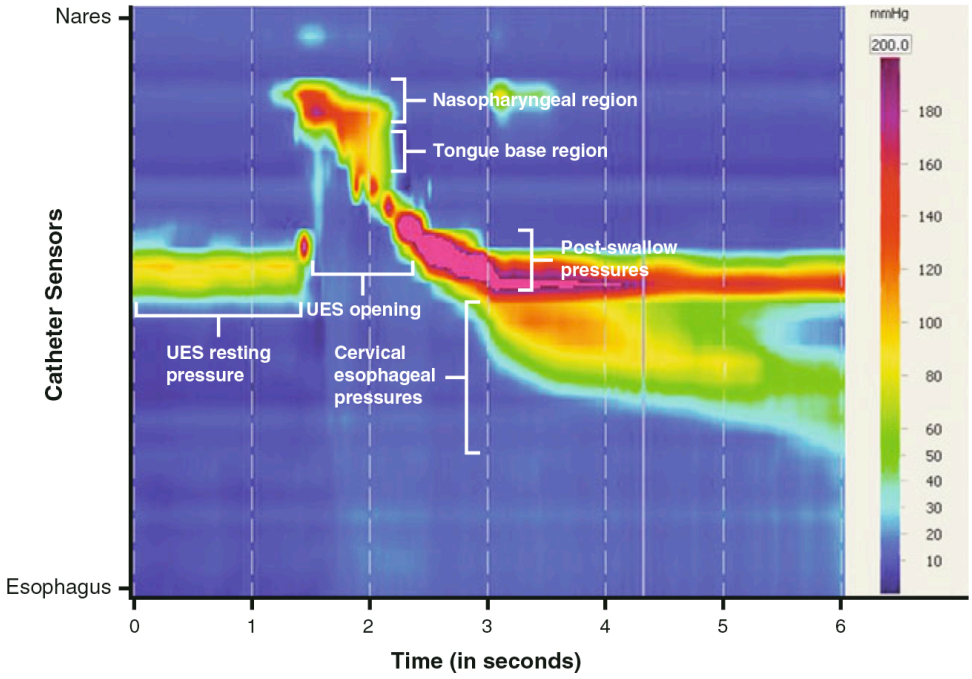


Figure 14.1 Sample spatiotemporal plot, with anatomic definitions provided to clinical users of pharyngeal HRM (Knigge et al., 2014; pp. 5).[11]

14.3.4 Data Analysis

Data were analysed using SPSS statistical software. ICC with absolute agreement definition were used to assess intra- and inter-rater reliability. Like other forms of reliability, there are

[11]Reprinted with permission of Springer Dysphagia, Implementation of high-resolution manometry in the clinical practice of speech language pathology., 29, 2014, 5, Knigge, M., Thibeault, S., McCulloch, T.

no standard values for acceptable reliability using ICC (Bruton et al., 2000) and, therefore, the criteria reported in Table 14.1 were utilized as comparison values (Portney & Watkins, 2008). As the nature of the tool determines the precision necessary to judge acceptable reliability, strict criterion levels were sought as HRM is a diagnostic tool.

Table 14.1 Portney et al. (2008) ICC criteria.

	Poor to Moderate	**Good**	**Desired (for clinical use)**
Criterion Level	< 0.75	0.75–0.90	> 0.90

14.3 Results

Ratings were analysed for all measures and all raters. Average amplitude and duration results are presented for the healthy participant (n = 3) and patient (n = 3) swallowing samples in Tables 14.2 and 14.3.

Table 14.2 Average amplitude (mmHg; SD) across swallowing features.

Swallowing feature	**Velopharyngeal pressure maximum**	**Tongue base pressure maximum**	**UES resting amplitude**	**UES nadir pressure**	**UES post-nadir maximum pressure**
Healthy (n=3)	132.4 (29.9)	149.9 (15.1)	41.6 (12.1)	-3.9 (4.7)	163.4 (34.3)
Patient (n=3)	73.9 (29.0)	105.5 (35.4)	30.4 (28.0)	-1.0 (4.3)	99.3 (35.6)

Table 14.3 Average duration (sec; SD) across swallowing features.

Swallowing feature	**Velopharyngeal pressure duration**	**Tongue base pressure duration**	**UES nadir duration**
Healthy (n=3)	1.0 (0.3)	1.0 (0.3)	0.7 (0.3)
Patient (n=3)	1.2 (0.5)	0.9 (0.4)	0.6 (0.2)

Overall, intra-rater reliability was high following training, with an average reliability of 0.99 (0.97–1.0). However, inter-rater reliability was highly variable across the amplitude and duration measurement domains. With regard to amplitude, as shown in Table 14.4, only two measures demonstrated clinically acceptable reliability, including velopharyngeal and tongue-base pressure maximums. The measures relevant to UES pressure amplitudes ranged

from poor to moderate, with UES nadir pressure being the least reliable measure between raters. With regard to duration, all measures were below clinical acceptability, as reported in Tables 14.4 and 14.5. Specifically, UES nadir duration had the lowest inter-rater reliability, with a range of 0.01–0.31.

Table 14.4 Inter-rater reliability of amplitude measurements.

Swallowing feature	Velopharyngeal pressure maximum	Tongue base pressure maximum	UES resting amplitude	UES nadir pressure	UES post-nadir maximum pressure
ICC	0.95	0.92	0.65	0.40	0.73
Range	0.90–0.98	0.86–0.97	0.46–0.82	0.14–0.67	0.51–0.87

Table 14.5 Inter-rater reliability of duration measurements.

Swallowing feature	Velopharyngeal pressure duration	Tongue base pressure duration	UES nadir duration
ICC	0.64	0.19	0.11
Range	0.42–0.82	0.04–0.42	0.01–0.31

14.4 Discussion

This study is the first to have evaluated the reliability of clinical swallowing measurements made with the Knigge et al. (2014) analysis method. This protocol is unique as it does not require exporting data to customized analysis programmes, largely inaccessible to users of pharyngeal HRM. The protocol uses existing system-based tools to evaluate important characteristics of pharyngeal swallowing, including duration and amplitude of pharyngeal swallowing across three anatomic areas of interest. Results indicate that, following training, intra-rater reliability was almost perfect. However, the majority of measures had unacceptable inter-rater reliabilities for use as a diagnostic tool in the clinical armamentarium (Portney & Watkins, 2008). Notably, results pertinent to UES measures, including UES nadir duration and nadir pressure, demonstrated the lowest inter-rater reliability. This is problematic, as HRM was designed to serve as an optimal evaluation method for investigation of UES function. Further, as compared to low-resolution manometry, the closely-spaced sensors inherent in HRM technology are optimally suited to evaluate the highly mobile UES during swallowing (Jones, Hammer, et al., 2014). As this technique is

commonly used pre- and post-treatment, be it behavioural or surgical, sound reliability is critical for appropriate use of this technique.

This variable reliability is considered to arise from reliably selecting anatomic landmarks and onset/offset points for durational measures. In standard HRM plots, the swallowing-related pressure is continuous along the catheter, without clear separation between defined regions. This is exacerbated by vague definitions provided by Knigge et al. (2014), reflecting the inherent anatomic variability across participants. Using the Smart Mouse^{TM} analysis tool, the user manually delineates a rectangle over the region of interest, from which the pressures are calculated across the sensors and over time. Therefore, if this box changes in dimensions across trials, variability in measurement is inherent. For example, the velopharynx is defined as "at least two channels" immediately above the tongue base region. As there is just one maximum pressure value in the velopharyngeal and tongue base regions, respectively, alteration in box size is unlikely to have a substantial effect on measurement. Further, pressures surrounding these areas of interest (e.g., resting pharyngeal structures) are unlikely to have competing maximal pressures in the absence of speech or cough. These two regions were found to have the highest reliability, demonstrating this point.

The same benefit of Smart Mouse^{TM} identification of maximum pressure is likely a notable limitation in identification of UES nadir pressure. For example, previous reports indicate that UES pressures can span a range of 4–6 sensors, with intra-swallow movement due to superior and anterior hyolaryngeal movement (Jones, Hammer, et al., 2014). Unlike maximum pressure measurement, if the Smart Mouse^{TM} user-delineated rectangle changes in dimension across trials, variability in measurement relating to UES function is pronounced. For example, identification of nadir pressure in the UES region is confounded by negative oesophageal pressures immediately inferiorly. The user must use caution to carefully inspect all sensors and values included within the analysis rectangle so that minimal values such as the resting pharyngeal pressure and nadir oesophageal pressures are not included. Coupled with difficulty in sensor selection, the low reliability of the UES region highlights its susceptibility to numerous sources of possible variability across raters. This finding is mirrored in a study by Lee et al. (2014) who investigated the correlation between visual and automated analysis of the UES using ManoView^{TM} system-based software. Although this study identified a strong correlation between visual and automated analysis for resting UES

pressure (correlation coefficient 0.99; 95% CI = 0.99–1.9), a poor correlation was found for UES relaxation duration (correlation coefficient = 0.29; 95% CI = 0.15–0.41). The authors stated "automated HRM UES relaxation parameter analysis is not accurate," and called for development of novel analysis techniques (Lee et al., 2014; p.480). As discussed in Chapter 7, normative data indicate that average nadir UES pressure of -4 mmHg has a narrow standard deviation of only 7 mmHg (Mielens et al., 2012). Therefore, the high variability between raters has pronounced diagnostic implications for evaluation of UES functioning on HRM.

The poor inter-rater reliabilities found in the present study indicate a critical need for further investigation of reliable analysis techniques. Fair-to-high inter-rater reliability reported by Jones et al. (2015) may reflect the importance of automation in analysis of these complex and variable, spatiotemporal plots. However, the automated analysis used by Jones et al. (2015) appears to be based upon similar anatomic definitions to those used by Knigge et al. (2014). While the individual can confirm the anatomic locations selected by the software, the higher reliability reported by Jones et al. (2015) may not equate to increased accuracy. The anatomic areas of interest, namely the velopharynx, tongue base (or mesopharynx) and UES, reduce the high-resolution information garnered from multiple, closely-spaced sensors to three averaged points of interest. The results become comparable to the output of low-resolution three-channel manometric systems, which report pressure and temporal data from three similar anatomic areas, namely superior pharynx, inferior pharynx and UES. By averaging across sensors and over time, the Knigge et al. (2014) and Jones et al. (2015) methods may be reducing the specificity of measurement and minimizing the advantages of HRM itself. Therefore, it is critical to consider validity of measures as well, especially with ongoing development of pharyngeal HRM automated measurement algorithms.

It is important to acknowledge the limitations of this study. The number of sample swallows could be increased in future research, to reflect more diverse patient presentations and bolus types, as prior publications have demonstrated poorer reliability with increasingly severity of dysphagic presentations (Tae Hee Lee et al., 2014). Further, a larger number of raters stratified across experience levels is necessary for a detailed analysis of real-world reliability after training. Lastly, this study was completed using existing ManoScan^{TM} software designed and optimized for oesophageal analysis. Ongoing research is needed for

modification of this software to accommodate the complex biomechanical nature of oropharyngeal swallowing. Access to system-based software with strong qualitative measurement properties, such as reliability and validity, is critical for clinical cross-over of this technique.

Chapter 15: Discussion of Methodological Studies

During execution of the behavioural studies in Part II, it became apparent that existing diagnostic methods were inadequate for understanding the rapid sensorimotor swallowing response. Pharyngeal manometry is the only method of quantifying pressure in the pharynx during swallowing, therefore a comprehensive understanding of the reliability and validity of this technique is critical for clinical cross-over. Therefore, these methodological studies provide preliminary evidence to further understand the measurement accuracies and best practices in use of both low- and high-resolution pharyngeal manometry.

Chapter 11 is the first study to have compared low- and high-resolution manometry. Advancements in the development of HRM have largely replaced a long history of manometric data collected with standardized unidirectional low-resolution catheters. Understanding differences in measurement between these two intraluminal pressure measurement devices is critical to explain the variability in normative data collected by similar intraluminal instruments. Significant differences in pressures were recorded between low- and high-resolution manometry. Importantly, there were significant differences in the measurement of peak-to-peak latency in dry swallowing conditions between low- and high-resolution manometry, both when using posterior-oriented unidirectional measurement or when averaging the low-resolution manometry data to approximate a circumferential recording. Further, there were significant differences between the duration of UES relaxation between conventional posterior-oriented low-resolution manometry to HRM in liquid swallowing, and with averaged low-resolution radial pressures and HRM in dry swallowing. It is unclear if these differences result from the increased diameter of the HRM catheter, or inherent differences in measurement. Ongoing research is critical to understand these measurement differences, as they are likely exacerbated in patient cohorts who present with unilateral asymmetries, for example. At the present time, it is unclear which manometric tool offers more accurate measures, thus it is clear both techniques warrant continued use in clinical practice and research of dysphagia.

Chapter 12 analysed possible measurement error in low- and high-resolution manometry. While low-resolution manometric measurements were stable over time, the substantial drift in the ManoScan™ HRM system was highly variable across sensors and studies and was not

corrected via standard operating instructions. This HRM drift can have a substantial impact in clinical diagnosis and research. For example, when evaluating function of the UES, normative data indicate that average nadir UES pressure of -4 mmHg has a narrow standard deviation of only 7 mmHg (Mielens et al., 2012). With a possible pressure drift of 6.5 mmHg in 15 min found in Chapter 12, caution is needed when interpreting acquired data and forming subsequent diagnoses. The standard TC process did not correct the error associated with the drift. ITC is able to correct the error associated with baseline drift, but requires communication with the manufacturer to enable this option. Overall pressure drift can have a substantial impact in clinical diagnosis and research of pharyngeal and oesophageal function and caution should be taken when referencing previously reported normative data. Published research using ManoScan^{TM} HRM instrumentation need to report what type of correction is implemented, if any, for accurate interpretation and replication of findings. Further research is indicated to evaluate if this measurement error is an inherent feature of other HRM measurement systems across manufacturers and thus pervasive across this technology.

Chapter 13 investigated the effects of TNA on tolerability and pharyngeal pressure using HRM. Results indicate TNA offered no difference in procedure comfort while affecting swallowing physiology; however, further research is warranted using larger diameter HRM catheters and oral (gargled) applications of anaesthetic. Larger diameter catheters may predispose the participant to increased discomfort, yet using additional anaesthetic, such as oral applications, may alter swallowing sensorimotor function to a greater degree. Results from this study may allow refinement of published protocols for conducting this examination and offer further information to guide best practice of pharyngeal HRM and similar trans-nasal intubation techniques. Given the cost, possible effect on swallowing sensorimotor function and limited improvement in procedure comfort, TNA is not essential in a procedural protocol for clinical manometric studies using 2.75-mm diameter catheters.

Lastly, Chapter 14 found the reliability of clinical swallowing measurements derived using the Knigge et al. (2014) protocol is substandard for clinical use. This is concerning given that the anatomic and measurement definitions proposed by Knigge et al. (2014) have been used in the majority of pharyngeal HRM studies to date. Further, the definitions in this protocol are being utilized in ongoing development of automated software programmes (Jones et al., 2015). Although intra-rater reliability was almost perfect after training, the majority of

measures had unacceptable inter-rater reliability. Users of pharyngeal HRM should therefore consider not only the limitations in reliability but the validity of measurements as well.

In conclusion, low- and high-resolution manometry have been further characterised with regard to reliability and validity. Low-resolution manometry appears reliable in terms of consistency across recording directions of unidirectional sensors and no apparent measurement error in response to temperature shock or study duration, unlike HRM. While advancements in HRM have overcome limitations in use of three-sensor low-resolution manometry, the results of the present work highlight ongoing limitations of HRM. Notably, there is a marked absence in analysis tools for HRM, with the only currently available published protocol demonstrating poor and variable reliability. Paired with the measurement error seen in the ManoScan^{TM} system, HRM should not be seen as the gold-standard as yet. There is a great need for ongoing research to further understand differences and indications for use of unidirectional versus circumferential catheters, differences in HRM systems and best-practice for analysis of pharyngeal swallowing on HRM. While manometry provides critical objective data at higher temporal resolutions than the widely-used technique of VFSS, a stringent review of reliability and validity of this technique is essential. In the short-term, further research is needed to improve the consistency of this system-based measurement for clinical use. Long-term research is needed for optimisation of novel analysis programmes that are specific to pharyngeal swallowing. This will likely have a substantial impact on diagnostics and best practice, as inclusion of pharyngeal manometry is key to comprehensive diagnostic assessment of oropharyngeal swallowing.

PART IV: CONCLUSION

Chapter 16: Conclusions and Future Research

This research programme was inspired by a desire to understand the neural underpinnings of an interesting patient cohort with an atypical presentation of dysphagia (Huckabee et al., 2014). In investigating their unique dysphagic presentation, questions emerged regarding the capability to volitionally alter discrete sequential elements of the overall motor plan of the pharyngeal phase of swallowing. Further, it was unknown if simultaneous pharyngeal pressure generation in the pharyngeal mis-sequencing cohort was representative of normal, non-ingestive, reflexive pharyngeal swallowing; perhaps the superior-to-inferior pattern is present only in volitional prandial ingestion (Huckabee et al., 2014). It became clear that our current understanding of central representation of swallowing is inadequate to account for the complexities in human deglutition.

This inadequacy likely reflected existing limitations in current diagnostic methods. Although manometry provides the temporal resolution to overcome limitation of other instrumentation, it has not been comprehensively investigated. Thus, this work investigated the reliability, validity and measurement accuracy of both low- and high-resolution pharyngeal manometry. Greater specificity in the evaluation of swallowing can increase confidence in differential diagnosis, such as identifying patients with pharyngeal mis-sequencing from those with reduced pharyngeal motility. This is critical, as risk of negative secondary outcomes, such as aspiration pneumonia, death and increased costs of care, are compounded should clinicians fail to identify or misdiagnose the swallowing impairment. The studies included in this programme of research have contributed to shortcomings in the literature regarding volitional modulation and the nature of underlying neural control of pharyngeal swallowing, as delineated in the subsequent section. While it remains clear the act of deglutition is highly complex, with greater specificity in the diagnosis and the fundamental understanding of swallowing neurophysiology, it is likely gains in best-practice to optimize patient outcomes will be within reach.

16.2 Review of Hypotheses

16.2.1 Behavioural Studies

Incidence, Aetiology and Pathophysiology of Pharyngeal Mis-sequencing in Dysphagic Patients with Neurologic Impairment

Two plausible, yet contrasting, hypotheses were posed, based on existing knowledge. While data collection remains ongoing, it is premature to definitively accept or reject either of these hypotheses. Nevertheless, the scant evidence collected to date indicates a trend toward pharyngeal mis-sequencing being a direct consequence of the neurologic deficit itself. Evidence supporting this hypothesis is the patient who presented with pharyngeal mis-sequencing at the initial data collection sections, with resolution in subsequent evaluations and no current evidence of mis-sequencing developing in patients in later evaluation sessions. While ongoing data collection is underway, there is no evidence of mis-sequencing in cortical-stroke or PD patients to date. Support for this hypothesis is further provided by patients who revert to a mis-sequenced pattern of swallowing when asleep, indicating the basic motor plan for their pharyngeal swallowing may be impaired at a reflexive level. Clearly, further research is needed to comment with greater confidence regarding the incidence, aetiology and pathophysiology of this unique dysphagic presentation.

Volitional Control of Pharyngeal Swallowing in Healthy Adults

Chapter 8 evaluated the capacity of healthy adults to modulate the latency of pressure generation between the proximal and distal pharynx. Participants had an effective limit in the capacity to reduce peak-to-peak latency in the temporal sequencing of pharyngeal swallowing, achieved through optimizing reduction in overall swallowing duration. It was hypothesized that normal healthy adults would be able to adopt a motor plan which recruits pharyngeal pressure in both the proximal and distal pharynx, with a substantially reduced peak-to-peak separation between pharyngeal manometric sensors following two weeks of daily biofeedback training. While this hypothesis was supported by the data, it contrasted to the secondary hypotheses, as reductions in peak-to-peak latency co-occurred with a simultaneous reduction in total swallowing duration. This suggests gains in volitional control of the latency of pharyngeal swallowing consisted of a more synergistic reduction in overall swallowing duration, rather than a shift in the discrete, elemental motor plan. The median peak-to-peak latency achieved by the healthy participants was above the 95% confidence interval of peak-to-peak latencies reported in the mis-sequencing patient group, suggesting

volitional modulation cannot alter the reflexive pharyngeal sequence to a pathologic level. This clarifies our initial hypothesis in that healthy adults may not be able to manipulate the basic pharyngeal motor plan, but may utilise existing volitional control to optimise a reduction of peak-to-peak latency by reducing overall swallowing duration.

Pharyngeal swallowing during wake and sleep states

Chapter 9 presented the first manometric investigation of pharyngeal biomechanics during sleep in healthy participants and patients with dysphagia. Results of differences in amplitude and latency of pharyngeal swallowing during sleep aligned with the hypothesis that normal healthy adults and patients with dysphagia will demonstrate a lower pressure amplitudes when asleep. However, results from the temporal analyses revealed no significant differences in latency or slope of pharyngeal pressure during sleep. This contrasts to findings of patients with dysphagia, who presented with a clear pattern of mis-sequenced pressure during sleep, even in the two patients who were able to sequence pressure adequately to enable functional swallowing when awake. This suggests that pharyngeal mis-sequencing is the result of neurologic impairment, highlighting the need for continued cortical contribution to maintain functional pharyngeal pressure latencies when awake in patients who demonstrate functional pharyngeal sequencing as a result of rehabilitation. This may provide additional data regarding the debate or the role of volition in swallowing motor control. This is of interest when considering understanding of pharyngeal swallowing and development of novel rehabilitation protocols. However, direct comparison of findings between healthy participants and patients with dysphagia is limited by lack of understanding of measurement differences in low- and high-resolution manometry.

16.2.2 Methodological Studies

A Comparison of Low- and High-resolution Pharyngeal Manometry

Understanding differences in measurement between these two intraluminal pressure measurement devices is critical to explain the variability in normative data collected by similar intraluminal instruments. Chapter 11 targeted this issue in with a within-subject comparison of low- and high-resolution manometry. Advancements in circumferential sensor technology enabled comparison of catheters with similar diameter (2.1 mm unidirectional diameter to 2.75 mm circumferential diameter). It was hypothesized that be no significant difference would be evidenced in the peak or nadir amplitude between the two sensor types.

This hypothesis was not supported by the data, with numerous significant differences between unidirectional and circumferential sensors, whether comparing posteriorly positioned measurements or an approximation of circumferential measurements by utilizing an average of unidirectional radial measurements. It was hypothesized that the unidirectional catheter would have longer latency of peak pharyngeal pressure generation between the levels of the upper and lower pharynx as compared to the circumferential catheter with no difference in the duration of UES relaxation. However, duration and amplitude were consistently longer and higher, respectively, with circumferential measurements. As HRM utilizes more than 12 measurement segments in each circumferential sensor, this paired with the slightly increased diameter could affect measurement consistency. Differences between measurement sensors were most notable in the UES, problematic for clinical users who rely on this technique for optimal evaluation of UES function. At the present time, it is unclear if low- or high-resolution manometry is superior. Due to the measurement differences seen between the two techniques, specific research is needed to understand which technique is optimal for certain evaluation parameters. It is likely that both instrumental devices will have continued relevance for evaluation of distinct parameters of pharyngeal swallowing, such as low-resolution manometry for evaluation of posterior pharyngeal peak-to-peak latency with increased specificity, while HRM may be more appropriate for evaluation of UES function.

Characterization and correction of measurement error in low- and high-resolution manometry: In-vitro and in-vivo

Chapter 12 reported a notable measurement error that refuted manufacturer report that pressure uniformity remains within 2 mmHg for 4 hr or less of recording. Further, overall drift was found to significantly vary between sensors and studies and is not corrected via the standard operating instructions utilizing ManoView™ software. This contrasts to low-resolution manometry, which demonstrated consistency in measurement over time. This is coupled with uncertainty in optimal best practice and analysis methods for pharyngeal HRM. It was postulated that, while there will be no measurement error in low-resolution manometry, there would be a significant measurement error in HRM, compensated appropriately by available correction methods. Findings supported the measurement consistency of low-resolution manometry but refuted the hypothesis by demonstrating pronounced measurement error in HRM varying between sensors and studies. The differences between measurement error in low- and high-resolution manometry may relate to sensor

design, as advancements in HRM technology have been criticized for contributing to measurement error (Babaei et al., 2015). More worryingly, this error was not corrected by standard processes, with use of a non-standard correct method recommended based on results. This will likely affect existing normative data, as it is unclear if the majority of HRM studies published to date have appropriately corrected for this measurement error.

The effect of topical nasal anaesthetic on tolerability and pharyngeal pressure in healthy adults: A double-blind study

Chapter 13 provided the first study to have investigated the effects of TNA on tolerability and pharyngeal pressure using HRM. Results indicate TNA provided no improvement in procedure comfort, with potential alterations in pharyngeal swallowing as compared to placebo conditions. While results from this study may allow refinement of published protocols for conducting this examination, future research is needed in the standard 4.2 mm adult HRM catheters, which may impact procedural comfort to a greater degree. Given the cost, limited benefit in procedure comfort, and possible effects on pharyngeal swallowing, it appears that TNA is not an integral component of routine examinations using a 2.75-mm HRM catheter.

Pharyngeal High-resolution Manometry: Reliability of Clinical Analysis of Swallowing

Chapter 14 is the first to have evaluated the reliability of clinical swallowing measurements from HRM. Results indicate that, following training, intra-rater reliability was almost perfect. However, the majority of measures had unacceptable inter-rater reliabilities for use as a diagnostic tool in the clinical armamentarium (Portney & Watkins, 2008). As this technique is commonly used pre- and post-treatment, be it behavioural or surgical, sound reliability is critical for appropriate use of this technique. This will likely have an impact on diagnostics and best practice, as further research is needed to standardize measurement of pharyngeal swallowing using HRM. While the Knigge et al (2014) clinical analysis protocol has substandard inter-rater reliability, sound intra-rater reliability will allow a single rater confidence to perform interpretation until more proficient analysis methods are developed and validated in HRM.

16.3 Critique

This research programme had limitations, which are important to acknowledge. As with many studies in the realm of swallowing physiology, this research was limited by small sample sizes, relying on largely young adults of European descent. Future research should implement similar research with larger sample sizes, a broader range of ages and more varied ethnicities to reflect patient populations to which this research relates. Additionally, all studies included in the present work utilized pharyngeal manometry, which does not directly allow full visualization of swallowing physiology. The number and type of swallows could be increased in future research, to reflect more diverse patient presentations and bolus types, as prior publications have demonstrated poorer reliability with increasingly severity of dysphagic presentations (Tae Hee Lee et al., 2014). Further research is indicated using manofluoroscopy to enable visual assessment of changes of biomechanics and bolus flow. Incorporation of VFSS could also provide insight on possible alteration of associated parameters, such as pharyngeal shortening as well as coordination with UES and laryngeal functioning. Further, as the manometric catheter was placed intraluminally, it is unknown how sensory feedback provided by the catheter may have affected results in studies described in Part II. As with any behavioural study, the studies in the present work, specifically Chapter 8 – the study of volitional control of swallowing using manometric visual biofeedback – are limited by brief evaluation sessions without follow-up. Thus ongoing data collection would be beneficial to determine the extent to which volitional control over pharyngeal swallowing may be increased or retained over time.

As described throughout the text, the behavioural studies were limited by methodological concerns described in Part III. By using system corrections of measurement error, for example, rather than the manual correction of measurement error in Chapter 9, results will likely be increasingly valid and replicable. Much work is needed in terms of reaching a consensus and, optimally, standardising analysis methods of pharyngeal HRM spatiotemporal plots. Without system-based analysis software to analyse HRM spatiotemporal plots, users may be inappropriately interpreting swallowing as evaluated by HRM with methodology used in prior work with low-resolution manometry. This affects current published protocols for clinical evaluation with HRM (Knigge et al., 2014) and further research is needed to update recommendations for best practice using pharyngeal HRM. A greater number of raters stratified across experience levels is necessary for a detailed analysis of real-world reliability

after training. Ongoing research is needed for modification of this software to accommodate the complex biomechanical nature of oropharyngeal swallowing. Access to system-based software with strong qualitative measurement properties, such as reliability and validity, is critical for clinical cross-over of this technique.

16.4 Future Work

This research programme provides the foundation for numerous future studies investigating both behavioural and methodological aspects of modulation of pharyngeal swallowing. Firstly, ongoing data collection is needed to complete the prospective, quantitative evaluation of pharyngeal mis-sequencing across patient populations is needed to further identify and characterize this atypical presentation of dysphagia. This prospective incidence study may not only further identify specific patient groups who exhibit pharyngeal mis-sequencing, but also explore the patterns of development of pharyngeal sequencing itself. Results from this study will assist clinicians in selecting appropriate diagnostic tools for dysphagic patients. Further, this study may also help guide management techniques, as commonly used therapeutic strategies may be contraindicated in this population (e.g., 'effortful swallow').

Additionally, although the present work further examined volitional modulation elements of the pharyngeal swallow, further research is needed to confirm whether humans are capable of modulating the select components of the pharyngeal swallow in isolation. Further research is indicated using manofluoroscopy to enable visual assessment of changes of biomechanics to quantify how a changes in pharyngeal sequencing affect swallowing parameters, if at all. Incorporation of VFSS can also provide insight on possible alteration of associated parameters during modulation of pharyngeal swallowing. It is critical to further understand the capability to fundamentally alter the pharyngeal motor plan, as this can generate novel avenues for rehabilitation of patients with dysphagia.

With advancements in manometry, further research is needed to understand the relationship between presence of an intraluminal catheter at various diameters in eliciting higher frequency of swallowing responses and subsequently altering swallowing biomechanics. Continued understanding of differences between manometric catheters and recording systems may help standardize measurement of pharyngeal swallowing using this instrumentation. Pharyngeal manometry is the only method of quantifying pressure in the pharynx during

swallowing and future research is needed to generate pathways to increase clinical application of this technique (Ravich, 1995). Prior to this, however, ongoing research is indicated to evaluate if measurement error is an inherent feature of other HRM measurement systems across manufacturers and thus pervasive across this technology. Replication of existing normative data is needed with HRM, as it is unclear if papers published to date have implemented the optimal data correction techniques. Further work is needed to determine which electromechanical mechanisms of HRM sensors lead to pressure drift. Previous publications have speculated that the catheter design may lend itself to deformation due to an air gap within the sensing membrane from a rigid surface of a metallic inner electrode (Babaei et al., 2012). With different metals in use, such as copper, the variable distortions following temperature shock at intubation may play a critical role in generating pressure drift. Although analog signals often have some level of baseline drift, how or why this baseline drift is variable across studies and between sensors is not known. Further investigation by the manufacturer is needed to understand the development of drift as a result of the intrinsic nature of the catheter. As there is notable variability both between sensors and across catheters, ongoing research investigating a greater number of catheters is warranted. Additionally, it is unclear how additional compensations, such as the weekly ManoScan™ in-vivo compensation are interacting with pressure drift and the related compensation methods.

A clear and precise understanding of swallowing biomechanics, and the neurophysiologic underpinnings of normal and disordered swallowing, are paramount to avoid negative secondary outcomes associated with dysphagia after neurologic impairment. Dysphagia resulting from neurologic impairment is a global health issue that will continue to escalate with an aging population. The prevalence of survivors of stroke alone are estimated to reach up to 77 million by the year 2030 (Donnan et al., 2008), with an annual lifetime cost of stroke estimated at $450 million (Stroke Foundation of New Zealand, 2009). Misdiagnosis of swallowing impairments places patients at an additional risk of worsening health status, above and beyond the risks already associated with neurologic impairment. This is non-negligible, as incidence of dying secondary to aspiration pneumonia has been identified at 5%, or 12,000 deaths per year in the United States (Chang et al., 2013). These statistics, importantly, can be reduced given optimal practice patterns and instrumental tools. However, for this research to be of benefit to patients, it must occur with tight clinical integration of

recommendations. As patients follow the continuum of care in stroke rehabilitation, streamlined, evidenced-based options for recovery are key, especially in the chronic stages. This is a critical to move practice forward in the comprehensive evaluation, and subsequent rehabilitation, of patients living with disability following stroke.

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APPENDICES

Appendix 1: Information Sheets and Consent Forms

Participant Information Sheet

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

Study title:	Incidence, Aetiology, and Pathophysiology of Pharyngeal Mis-sequencing in Dysphagic Patients with Neurologic Impairment		
Locality:	Canterbury District Health Board	**Ethics committee ref.:**	13/STH/179
Lead investigator:	Dr Maggie-Lee Huckabee	**Contact phone number:**	(+64 03) 364 2307

You are invited to take part in a study investigating swallowing difficulty in people with brain damage. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you agree to take part, but change your mind, you can pull out of the study at any time.

This information sheet will help you decide if you'd like to participate. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what happens after the study ends. We will go through the information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with others, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page. You will be given a copy of both the Information Sheet and the Consent Form to keep. This document is 7 pages long, including the Consent Form. Please make sure you read and understand everything.

WHAT IS THE PURPOSE OF THE STUDY?

We are interested in a certain type of swallowing problem where people mis-sequence the timing of their swallow. This makes it difficult to safely eat and drink. So, we want to observe who develops mis-sequenced swallowing, and when this develops after brain injury. This study will recruit 100 patients from two hospitals (Christchurch Hospital and Singapore Hospital) over a period of 18 months. Patients with four medical conditions will be recruited: cortical stroke, brainstem stroke, Parkinson's disease, and brain tumours.

The supervising investigator is Dr. Maggie-Lee Huckabee. She has a Ph.D. in Speech Pathology. She has worked in the area of swallowing disorders for 29 years, and is a senior lecturer in the Department of Communication Disorders, and senior researcher at the New Zealand Brain Research Institute.

The researching investigator is Kristin Lamvik. She is a Ph.D. Student at the University of Canterbury who has a Master of Science degree in Medical Speech-Language Therapy. She has worked with patients in an acute care hospital setting for two years.

You can contact the researching investigator, Kristin Lamvik, during work hours at (03) 378 6348 or anytime via email at kristin.lamvik@pg.canterbury.ac.nz

This study will be funded by the Swallowing Rehabilitation Research Laboratory from the New Zealand Brain Research Institute. This study has been reviewed and approved by The Health and Disability Ethics Committees (HDECs). If you have any questions or concerns regarding the ethical aspects of this study please contact:

The Health and Disability Ethics Committees (HDECs)
Ministry of Health
No 1 The Terrace
PO Box 5013
Wellington
0800 4 ETHICS (438 442)
hdecs@moh.govt.nz

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

You are being recruited for this study after being referred by your doctor for an x-ray of your swallowing (called *videofluoroscopic swallowing study*). We will organise the time with your doctors so that it does not interfere with your clinical care. You can be selected to participate if you are older than 18 years old, and have no medical problems that may affect your swallowing. The evaluation session will take approximately one hour, and will be repeated three times over six months if you are able.

If you agree to take part in this study, the pressure in your throat will be evaluated when you swallow with a technique called manometry. When you are ready to start, you will be seated in a comfortable chair. One of the investigators will place a thin tube (2.1 mm in diameter) in your nose. As the tube reaches the top of your throat, you will be instructed to repeatedly swallow the tube into the throat. The tube will then be slowly pulled up until it is correctly placed in your throat and taped to your nose. We will ask you to do 5 saliva swallows, three 10 ml drinks of liquid and three 10ml bites of applesauce. Then the tube will be removed from your nose. Your swallowing x-ray may continue after the tube is removed. Health information will be collected by questionnaires and by accessing medical records. The questionnaires will ask you how your swallowing impacts your daily life. You will be given a code number so that your name and personal information will be removed from all paperwork, and the data will be kept in locked storage at a research institute for 10 years.

SCHEDULE OF VISITS AND PROCEDURES:

The stroke group will be seen at the same time during your swallowing x-ray, ordered by your doctor. If you do not participate in this study, you will still have your swallowing x-ray (without manometry).

As stroke is an unplanned event, you cannot be evaluated before these conditions develop. Also, as many cortical stroke patients are likely unable to participate in follow-up sessions due to transport and accessibility challenges, only one planned data collection session will be scheduled during your hospital stay.

Follow-up Intervals for the Stroke Groups

Brainstem Stroke Group	Cortical Stroke Group
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One week following stroke	One week following stroke
1 month after admission with stroke	Follow-up if presenting with swallowing problems depending on accessibility
3 months after admission with stroke	
6 months after admission with stroke	

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

There are no documented complications of using the small 2.1 mm manometry tube. It is used commonly in clinic and research. However, there have been complications reported with a larger 3.5 mm tube (not used in this study). These include discomfort, nose bleeds, rare instances of fainting, rare instances of spasm of the muscles in the larynx or voice box, changes in heart rate or blood pressure, and oxygen desaturation.

The swallowing x-ray (videofluoroscopy) exposes you to small doses of radiation. Though the first exam will be performed as part of routine clinical care as ordered by your doctor, the follow-up examinations are likely not part of routine clinical care and will expose you to small doses of extra radiation. However, the radiation dose during swallowing x-rays is much lower than that of a routine chest CT, and more than 40 swallowing x-rays would be needed in a year to exceed the annual radiation exposure dose limit.

The benefits of this study are detailed evaluation of your swallowing function over time. You will be monitored very carefully by the researchers for any changes during this study. Facilities for emergency medical management are available where the experiment is completed at Canterbury District Health Board.

WHO PAYS FOR THE STUDY?

This study will be paid for by the University of Canterbury Swallowing Rehabilitation Research Lab. You will not have any costs participating in this study. No forms of payment will be provided for participating.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you would be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery. If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT ARE MY RIGHTS?

Your participation is voluntary. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

You have the right to access information about yourself collected as part of the study. You will be told of any new information about adverse or beneficial effects related to the study that may have an impact on your health

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

If you agree to take part in this study, you are free to withdraw at any time, without having to give a reason. This will in no way affect any future care or treatment. If we discover a swallowing problem, you will be referred to a speech-language pathologist for follow-up. If you are identified with mis-sequenced swallowing, you will be invited to participate in a trial treatment study at no cost to you.

The data may be included in the investigator's PhD thesis. With your permission, data from this study may be used in future related studies, which have been given ethical approval from the Health and Disability Ethics Committees (HDECs). It is possible that data may be submitted for publication to a peer-reviewed journal. However, no material which could personally identify you will be used in any reports on this study.

Consent forms will be kept in a locked filing cabinet in the locked swallowing research laboratory or will be stored on password-protected laboratory computers. Research data will be stored for a period of 5 years after data collection, after which they will be destroyed.

You will be offered copies of the final manuscript or a summary. However, you should be aware that a long delay may occur between completion of data collection and the final

report. Alternatively, or in addition, you can choose to have the results of the study discussed with you personally by the principal investigator.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you need an interpreter, this can and will be provided.

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Kristin Lamvik
PhD Candidate
(03) 364 2307
kristin.lamvik@pg.canterbury.ac.nz

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz

Consent Form

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

If you need an INTERPRETER, please tell us.

Please tick to indicate you consent to the following

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.	Yes ☐	No ☐
I have been given sufficient time to consider whether or not to participate in this study.	Yes ☐	No ☐
I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.	Yes ☐	No ☐
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.	Yes ☐	No ☐
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.	Yes ☐	No ☐
I consent to the research staff collecting and processing my information, including information about my health.	Yes ☐	No ☐
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐	No ☐
I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study.	Yes ☐	No ☐
I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.	Yes ☐	No ☐
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.	Yes ☐	No ☐

I understand the compensation provisions in case of injury during the study.	Yes ☐	No ☐
I know who to contact if I have any questions about the study in general.	Yes ☐	No ☐
I understand my responsibilities as a study participant.	Yes ☐	No ☐
I wish to receive a summary of the results from the study.	Yes ☐	No ☐

Declaration by participant:
I hereby consent to take part in this study.

Participant's name: _____

Signature: _____ Date: _____

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name: _____

Signature: _____ Date: _____

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

INFORMATION SHEET

Research Title:

The capacity for cortical control of pharyngeal swallowing in healthy adults

Principal Investigator:

Kristin Lamvik

Ph.D. Candidate, Department of Communication Disorders

University of Canterbury

New Zealand Brain Research Institute

66 Stewart Street, Christchurch, New Zealand

(03) 378 6348

Co-Investigators:

Maggie-Lee Huckabee, PhD

Senior lecturer, Department of Communication Disorders

University of Canterbury

New Zealand Brain Research Institute

66 Stewart Street, Christchurch, New Zealand

(03) 378 6070

Other Investigators:

Sonja Kaulmann

Visiting Research Clinician

New Zealand Brain Research Institute

66 Stewart Street, Christchurch, New Zealand

Introduction and aims of the project:

You are invited to participate in a research project that investigates the timing of swallowing in healthy adults. The aim of the study is to evaluate to determine if healthy participants, upon completion of a training protocol, can learn to change the timing of pressure made by the tongue and throat muscles during swallowing.

Taking part in this study is voluntary (your choice) and you can withdraw from the study at any time. Any decision not to participate will not affect your current, continuing or future health care or academic progress. We would appreciate a decision regarding your participation within two weeks. This research is part of the principal investigator's Ph.D. (Doctor of Philosophy) project.

Participant selection:

Your participation in this study is due to your reply to advertisements for research participants. Upon your consent, you will be selected for this study if you are aged between 18 and 65, and have no medical problems that may affect your swallowing. The study will include a total of 6 participants of the same age group who have no swallowing problems and will require 10 session of approximately 1 hour duration.

The research procedure:

The research will take place at the New Zealand Brain Research Institute. If you agree to participate in the study, the following will occur:

1. You will be given an appointment and asked to come to the Swallowing Rehabilitation Research Laboratory at the New Zealand Brain Research Institute, 66 Stewart Street, Christchurch.
2. The consent form will be verbally reviewed, and you can sign if you meet the inclusion criteria to participate in the study.
3. At the beginning of the session, you will be shown visual images of manometric waveforms depicting normal pharyngeal pressure during swallowing. You will be briefly educated regarding the goal of the treatment session, which is to reduce the separation between the peaks of the upper and lower sensors.
4. Following your acknowledgment of understanding, manometry will begin. You will be seated in a comfortable chair and the researcher will ask you if you are ready to start. A manometry catheter (2.1 mm in diameter) will be placed in your nose. As the

catheter reaches the top of your throat, you will be instructed to repeatedly swallow water via straw. In doing so, the catheter will be swallowed into the esophagus. The catheter will then be slowly pulled out of your nose so the sensors are correctly placed in your throat when you swallow. The catheter will then be taped securely to the external nose with adhesive tape.

5. You will be asked to perform five dry swallows, without visualization of the waveform, to gather baseline data. Then you will be instructed to "try to make your waveforms overlap" while watching the live manometric recording data on a screen.
6. Each session will consist of three fifteen minute blocks of training, performing dry swallows at a self-generated pace, approximately one swallow every 30-45 seconds. Sips of water will be offered as needed to moisten the mouth. On completion of the three blocks of training, the catheter will be removed from the nasopharynx and the session will be terminated for that day.
7. No audio- or video-recordings of the testing session will be made. The only data recorded will be the line tracings that represent the pressure in your throat. Confidentiality will be assured by assigning you a coded numerical identification and data will be stored in the locked Swallowing Rehabilitation Research Laboratory at New Zealand Brain Research Institute.

Risks and Benefits:

Unfortunately we cannot offer any token to you for appreciation in our study. The only benefit to you is that your participation contributes important information regarding the cortical control mechanisms of swallowing.

There are no documented complications of pharyngeal manometry using this small 2.1 mm diameter catheter. It is used commonly in clinical and research settings in both normal and impaired participants. However, reported potential complications of evaluations with a larger 3.5 mm diameter endoscope include patient discomfort, nose bleeds, inadvertent stimulation of the true vocal folds, rare instances of fainting, rare instances of laryngospasm (or spasm of the muscles in the larynx or voice box), changes in heart rate or blood pressure, and oxygen desaturation.

You will be monitored very carefully by the researchers for any negative outcomes arising from your participation in this study. Facilities for emergency medical management, including suctioning and intubation, are available in the Swallowing Research Laboratory

where the experiment is completed. Further medical help will be available from the patient care wards and the Emergency Cardiac Response team at hospital should any complications arise.

Compensation:

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention, Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigator. If you have questions about ACC, contact your nearest ACC officer or the investigator.

Participation:

If you do agree to take part in this study, you are free to withdraw at any time, without having to give a reason. This will in no way affect any future care or treatment. Your participation in the study will be stopped should any harmful effects appear or if you feel it is not in your best interest to continue.

Confidentiality:

These exploratory data may be included in the investigator's PhD thesis. With your permission, data from this study may be used in future related studies, which have been given ethical approval from a Health & Disability Ethics Committee. It is possible that data will provide the foundation for a subsequent research trial or may be submitted for publication to a peer-reviewed journal. However, no material which could personally identify you will be used in any reports on this study. Consent forms will be kept in a locked filing cabinet in the locked swallowing research laboratory or will be stored on password-protected laboratory computers. Research data will be stored for a period of 10 years after data collection is completed, at which time they will be destroyed.

Results:

You will be offered copies of the final manuscript of this project or a summary in lay language. However, you should be aware that a significant delay may occur between completion of data collection and the final report. Alternatively, or in addition, you can choose to have the results of the study discussed with you personally by the principal investigator.

Questions:

You can contact the principal investigator if you require any further information about the study. The principal investigator, Kristin Lamvik, can be contacted during work hours at (03) 3786348 or via email: kristin.lamvik@pg.canterbury.ac.nz

If you need an interpreter, this can and will be provided.

If you have any questions or concerns about your rights as a participant in this research study, you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act.

Telephone (NZ wide): 0800 555 050

Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT)

Email (NZ wide): advocacy@hdc.org.nz

This study has been reviewed and approved by the UC Human Ethics Committee. If you have any questions or concerns regarding the ethical aspects of this study please contact:

Human Ethics Committee
Okeover House

Christchurch 8140

Telephone: 45588 or 03 364 2987

Email: human-ethics@canterbury.ac.nz

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

The capacity for cortical control of pharyngeal swallowing in healthy adults

CONSENT FORM

I have been given a full explanation of this project and have been given an opportunity to ask questions. I understand what will be required of me if I agree to take part in this project. I understand that my participation is voluntary and that I may withdraw at any stage without penalty.

I understand that any information or opinions I provide will be kept confidential to the researcher and that any published or reported results will not identify me. I understand that all data collected for this study will be kept in locked and secure facilities at the New Zealand Brain Research Institute and will be destroyed after five years.

I understand that if I require further information I can contact the researcher, Kristin Lamvik.
If I have any complaints about the research, I can contact the University of Canterbury Human Ethics Committee.

I agree that Dr. Maggie-Lee Huckabee, Kristin Lamvik or Sonja Kaulmann will perform the catheter insertion.

- Dr Maggie-Lee Huckabee has a Ph.D. in Speech Pathology. She practiced as a clinician for 13 years, is a senior lecturer in the Department of Communication Disorders, and senior researcher at the New Zealand Brain Research Institute.
- Kristin Lamvik is a Ph.D. Student at the University of Canterbury who has a Master of Science degree in Medical Speech-Language Therapy and a certificate of clinical competence in Speech Language Pathology from the American Speech-Language-Hearing-Society. She has worked with patients in an acute care hospital setting for two years.
- Sonja Kaulmann is a visiting Speech Language Therapist and trained Nurse from Germany. She worked at the Intensive Care Unit in a German hospital for four years.

By signing below, I agree to participate in this research project.

Print Name of Participant _____

Signature of Participant _____

Date _____

Day/month/year

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of the information sheet has been provided to the participant.

Print Name of Researcher/person taking the consent _____

Signature of Researcher /person taking the consent _____

Date _____

Day/month/year

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Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

INFORMATION SHEET

Research Title:
Pharyngeal pressure in healthy adults: the effect of topical nasal anaesthetic and characterization of swallowing during sleep.

Principal Investigator:
Kristin Lamvik
Ph.D. Candidate, Department of Communication Disorders
University of Canterbury
New Zealand Brain Research Institute
66 Stewart Street, Christchurch, New Zealand
(03) 378 6348

Supervisor:
Maggie-Lee Huckabee, PhD
Senior lecturer, Department of Communication Disorders
University of Canterbury
New Zealand Brain Research Institute
66 Stewart Street, Christchurch, New Zealand
(03) 378 6070

Prof Richard Jones
Neuroscientist & Neuroengineer
University of Canterbury
New Zealand Brain Research Institute
66 Stewart Street, Christchurch, New Zealand
(03) 378 6077

Co-Investigators:
Dr Olivia Apperley
Oral Health Centre
Christchurch Hospital
2 Riccarton Ave, Christchurch, New Zealand
(03) 364 0250

Introduction and aims of the project:

You are invited to take part in a research project that evaluates swallowing using a procedure called manometry. Manometry is a thin, bendable tube with pressure sensors that are put in your nose and down your throat. This lets us measure changes in throat pressure when swallowing.

There are two goals of this study. The first is to see if numbing the nose changes your comfort during the process or changes the way you swallow. This information will tell us if using numbing is the best way to perform this test. Secondly, we are interested in evaluating swallowing when asleep, as compared to when awake. This part of the study will give us information about how the thinking part of your brain controls swallowing.

Taking part in this study is voluntary (your choice) and you can withdraw from the study at any time. Any decision not to participate will not affect your current, continuing or future health care or academic progress. We would appreciate a decision regarding your participation within two weeks. This research is part of the principal investigator's Ph.D. (Doctor of Philosophy) project.

Participant selection:

Your participation is due to your reply to flyers. You can join this study if you are 18 years or older, and have no medical problems that may affect your swallowing. The study will include a 20 healthy adults who have no swallowing problems, and will require 2 sessions. The first session will last approximately 30 min, and the second session will be an overnight sleep study of approximately 8 hr of time.

The research procedure:

The research will take place at the New Zealand Brain Research Institute. If you agree to participate, here is what will happen:

1. We will explain the consent form at the beginning of the first session, and you can sign if you want to participate. We will talk about the manometry method and answer any questions.

2. Once all your questions have been answered and you agree to participate, manometry will begin. You will be seated in a comfortable chair and the researcher will ask you if you are ready to start. Either 0.4 ml of 2% viscous lidocaine hydrochloride (numbing gel) or plain lubricant will be applied by a licensed dental surgeon to one side of your nose, for one minute each time, via a cotton-tip applicator. A manometry tube (2.75 mm thick) will be placed in your nose by the researcher. As the tube reaches the top of your throat, you will be instructed to repeatedly swallow water from a straw. This will help the tube be swallowed into the oesophagus. The tube will then be slowly pulled out of your nose so the sensors are correctly placed in your throat when you swallow and then taped securely to your nose with adhesive tape.

3. You will be asked to perform five saliva swallows, at your own pace. Sips of water will be offered as needed to moisten your mouth. After this, you will be asked to swallow five 10 mL sips of water. Then, you will rate how the procedure felt using a rating scale, from '0' (no discomfort) to '10' (extreme discomfort). The tube will then be removed from your nose by quickly pulling it out.
4. The next day, you will return for the sleep study. You will receive a different nasal numbing condition than the day before. Either 0.4 ml of 2% viscous lidocaine hydrochloride (numbing gel) or plain lubricant will be applied by a licensed dental surgeon to one side of the nose, depending on what you received in the first session, one minute each time, via a cotton-tip applicator. The same procedure will be used to insert the manometry tube. You will be asked to perform five saliva swallows, and then swallow five 10 mL sips of water, at your own pace. Then, you will rate how the procedure felt using a visual rating scale, from '0' (no discomfort) to '10' (extreme discomfort). Again, information about how you swallowed will be stored on the computer and analysed at another time.

5. You will then get in a comfortable position in bed. You will be left alone to fall asleep. The researchers will remain outside the room watching the live recordings of

your swallowing throughout the night. If you need to wake up at any time (e.g., to go the restroom), the cord can be unplugged from the computer so we can leave the tube in your nose, and easily plug the cord in when you return (without having to put the tube in and out of your nose). There is a private security company monitoring the laboratory during the night, and there will always be more than one researcher present during the evening study for safety. You will be woken up at 6:00am the following morning, and the tube will be removed from the nose. Then the study will be complete.

6. No audio- or video-recordings of the testing session will be taken. The only data recorded will be the line tracings that represent the pressure in your throat and the comfort scale that you complete at both sessions.
7. We will keep your data confidential by giving you a number code that is private and not using any identifying labels (e.g., your name or birthday). Data will be stored in the locked Swallowing Rehabilitation Research Laboratory at New Zealand Brain Research Institute.

Risks and Benefits:

We can offer you a $10 travel voucher to reimburse you for petrol costs. Unfortunately we cannot offer you any further token of appreciation for participation. The only benefit to you is that your participation gives important information about swallowing in healthy adults.

There are no known problems of pharyngeal manometry using 2.75 mm diameter tubes. It is used commonly in clinical and research settings in both normal and impaired participants. However, reported potential complications of evaluations with a larger 3.5 mm diameter endoscope include patient discomfort, nose bleeds, inadvertent stimulation of the vocal folds, rare instances of fainting, rare instances of spasm of the muscles in the voice box, changes in heart rate or blood pressure, and oxygen desaturation. There are also rare, yet possible, risks associated with topical nasal anaesthetic, such as stinging, swelling, slow/shallow breathing, slow/irregular heartbeat, or allergic reactions. These risks will be reduced by having a licensed dental surgeon prepare, apply, and monitor your response to the mild numbing solution.

You will be monitored very carefully by the researchers for any negative outcomes during your participation in this study. Facilities for emergency medical management, including suctioning and intubation, are available in the Swallowing Research Laboratory where the experiment is completed. Further medical help will be available from the patient care wards and the Emergency Cardiac Response team at hospital should any complications arise.

Compensation:

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention, Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigator. If you have questions about ACC, contact your nearest ACC officer or the investigator.

Participation:

If you do agree to take part in this study, you are free to withdraw at any time, without having to give a reason. This will in no way affect any future care or treatment, or academic participation if you are a student. Your participation in the study will be stopped should any harmful effects appear or if you feel it is not in your best interest to continue. Once you have completed the sleep study portion of the project, you can no longer remove your data from analysis, as we will remove your name and identifying information at that point in time.

Confidentiality:

These exploratory data may be included in the investigator's PhD thesis. With your permission, data from this study may be used in future related studies, which have been given ethical approval from a Health & Disability Ethics Committee. It is possible that data will provide the foundation for a subsequent research trial or may be submitted for publication to a peer-reviewed journal. However, no material which could personally identify you will be used in any reports on this study. Consent forms will be kept in a locked filing cabinet in the

locked swallowing research laboratory or will be stored on password-protected laboratory computers. Research data will be stored for a period of 10 years after data collection is completed, at which time they will be destroyed.

Results:

You will be offered copies of the final manuscript of this project or a basic summary. However, you should be aware that a significant delay may occur between completion of data collection and the final report. Alternatively, or in addition, you can choose to have the results of the study discussed with you personally by the principal investigator.

Questions:

You can contact the principal investigator if you require any further information about the study. The principal investigator, Kristin Lamvik, can be contacted during work hours at (03) 378 6070 or via email: kristin.lamvik@pg.canterbury.ac.nz

If you need an interpreter, this can and will be provided.

If you have any questions or concerns about your rights as a participant in this research study, you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act.

Telephone (NZ wide): 0800 555 050
Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT)
Email (NZ wide): advocacy@hdc.org.nz

This study has been reviewed and approved by the UC Human Ethics Committee. If you have any questions or concerns regarding the ethical aspects of this study please contact:

Human Ethics Committee
Okeover House
Christchurch 8140
Telephone: 45588 or 03 364 2987
Email: human-ethics@canterbury.ac.nz

Pharyngeal pressure in healthy adults: the effect of topical nasal anaesthetic and characterization of swallowing during sleep.

CONSENT FORM

I have been given a full explanation of this project and have been given an opportunity to ask questions. I understand what will be required of me if I agree to take part in this project. I understand that my participation is voluntary and that I may withdraw at any stage without penalty.

I understand that any information or opinions I provide will be kept confidential to the researcher and that any published or reported results will not identify me. I understand that all data collected for this study will be kept in locked and secure facilities at the New Zealand Brain Research Institute and will be destroyed after ten years.

I understand that if I require further information I can contact the researcher, Kristin Lamvik, or her supervisor, Dr Maggie-Lee Huckabee. If I have any complaints about the research, I can contact the University of Canterbury Human Ethics Committee.

I agree that one of the researchers, either Dr. Maggie-Lee Huckabee or Kristin Lamvik, will perform the catheter insertion.

- Dr Maggie-Lee Huckabee has a Ph.D. in Speech Pathology. She practiced as a clinician for 13 years, is a senior lecturer in the Department of Communication Disorders, and senior researcher at the New Zealand Brain Research Institute.
- Kristin Lamvik is a Ph.D. Student at the University of Canterbury who has a Master of Science degree in Medical Speech-Language Therapy and a certificate of clinical competence in Speech Language Pathology from the American Speech-Language-Hearing-Society. She has worked with patients in an acute care hospital setting for two years.

By signing below, I agree to participate in this research project.

Date _____

Print Name of Participant _____

Signature of Participant _____

Date of Birth _____

Would you like to receive a summary of the research findings? (Choose one) Yes_____ No_____

Email: _____ or Mailing Address: _____

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of the information sheet has been provided to the participant.

Print Name of Researcher/person taking the consent _____

Signature of Researcher /person taking the consent _____

Date _____

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

INFORMATION SHEET

Research Title:
Pharyngeal pressure in healthy adults: Comparison of unidirectional versus circumferential measures.

Principal Investigator:
Kristin Lamvik
Ph.D. Candidate
Communication Disorders
University of Canterbury
(03) 364 2307

Supervisor:
Dr Maggie-Lee Huckabee
Communication Disorders
University of Canterbury
(03) 362 2014

Co-Supervisor:
Prof Richard Jones
Communication Disorders
University of Canterbury
(03) 378 6077

Introduction and aims of the project:
You are invited to take part in a study investigating swallowing using a procedure called manometry. Manometry is a thin, bendable tube with pressure sensors that are put in your nose and down your throat. This lets us measure throat pressure when swallowing. Manometry has two types of sensors – one that records only in one direction (unidirectional) and the other that records from all sides (circumferential).

The purpose of this research is to get more information about how these two types of sensors differ. The sensors measuring only one direction have been used clinically to evaluate people with swallowing problems since the early 1990's. However, with the use of newer sensors that measure from all sides (circumferential), it is unclear how this changes our understanding throat pressure when swallowing. The benefits of this study to the wider clinical community include further understanding of how these two types of sensors differ, and how this relates to our understanding of swallowing. This may help in future studies of people with swallowing problems, giving clinicians more information about how the two measurement devices differ, and which may lead to a more accurate evaluation of swallowing.

Taking part in this study is your choice and you can withdraw from the study at any time. Any decision not to participate will not affect your current, continuing or future health care or academic progress.

Participant selection:
You can join this study if you are 18 years or older, and have no medical problems that may affect your swallowing.

The research procedure:
The research will take place at the New Zealand Brain Research Institute. If you agree to participate, here is what will happen:

8. The study will include 10 healthy adults who have no swallowing problems, and will require one session lasting about an hour. We will explain the consent form at the beginning of the first session, and you can sign if you want to participate. We will talk about the manometry method and answer any questions.
9. Once all your questions have been answered and you agree to participate, manometry will begin. You will be seated in a comfortable chair and the researcher will ask you if you are ready to start. The researcher will put 0.4 ml plain lubricant to one side of your nose, via a cotton-tip applicator. A manometry tube (2.21 mm thick) will be placed in your nose by the researcher. As the tube reaches the top of your throat, you will be instructed to repeatedly swallow water from a straw. This will help the tube be swallowed into the oesophagus. The tube will then be slowly pulled out of your nose so the sensors are correctly placed in your throat when you swallow and then taped securely to your nose with adhesive tape.

10. You will be asked to perform ten saliva swallows, at your own pace. Sips of water will be offered as needed to moisten your mouth. We will then spin the catheter so it faces different directions in your throat. You will swallow 10 times for each direction. The tube will then be removed from your nose by quickly pulling it out.
11. Then, we will begin the second evaluation after a break of about 10 minutes or longer if you prefer. You will have a different catheter (2.75 mm thick). The same procedure will be used to insert the manometry tube, as written above. You will be asked to perform 10 saliva swallows at your own pace. The tube will then be removed from your nose by quickly pulling it out, and your participation in the study will be complete.
12. Information about how you swallowed will be stored on the computer and analysed at another time. The only data recorded will be the line tracings that represent the pressure in your throat; no audio- or video-recordings of the testing session will be taken

Risks and Benefits:
Unfortunately we cannot offer you any further token of appreciation for participation. The only benefit to you is that your participation gives important information about swallowing in healthy adults.

There are no known problems of pharyngeal manometry using 2.21 or 2.75 mm diameter tubes. It is used commonly in clinical and research settings in both normal and impaired participants. However, reported potential complications of evaluations with a larger 3.5 mm diameter endoscope include

patient discomfort, nose bleeds, inadvertent stimulation of the vocal folds, rare instances of fainting, rare instances of spasm of the muscles in the voice box, changes in heart rate or blood pressure, and oxygen desaturation. You will be monitored very carefully by the researchers for any negative outcomes during your participation in this study. Facilities for emergency medical management, including suctioning and intubation, are available in the Swallowing Research Laboratory where the experiment is completed. Further medical help will be available from the patient care wards and the Emergency Cardiac Response team at hospital should any complications arise.

Compensation:
In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention, Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigator. If you have questions about ACC, contact your nearest ACC officer or the investigator.

Participation:
If you do agree to take part in this study, you are free to withdraw at any time, without having to give a reason. This will in no way affect any future care or treatment, or academic participation if you are a student. Your participation in the study will be stopped should any harmful effects appear or if you feel it is not in your best interest to continue. Once you have completed the first session of the project, you can no longer remove your data from analysis, as we will remove your name and identifying information at that point in time.

Confidentiality:
These exploratory data may be included in the investigator's PhD thesis. It is possible that data will provide the foundation for a subsequent research trial or may be submitted for publication to a peer-reviewed journal. However, no material which could personally identify you will be used in any reports on this study. Consent forms will be kept in a locked filing cabinet in the locked swallowing research laboratory or will be stored on password-protected laboratory computers. Research data will be stored for a period of 10 years after data collection is completed, at which time they will be destroyed.

Results:
You will be offered copies of the final manuscript of this project or a basic summary. However, you should be aware that a significant delay may occur between completion of data collection and the final report. Alternatively, or in addition, you can choose to have the results of the study discussed with you personally by the principal investigator.

Questions:
You can contact the principal investigator if you require any further information about the study. The principal investigator, Kristin Lamvik, can be contacted during work hours at (03) 378 6070 or via email: kristin.lamvik@pg.canterbury.ac.nz

If you need an interpreter, this can and will be provided. If you have any questions or concerns about your rights as a participant in this research study, you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act.

Telephone (NZ wide): 0800 555 050
Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT)
Email (NZ wide): advocacy@hdc.org.nz

This study has been reviewed and approved by the UC Human Ethics Committee. If you have any questions or concerns regarding the ethical aspects of this study please contact:

Human Ethics Committee
University of Canterbury
Private Bag 4800
Christchurch
Email: human-ethics@canterbury.ac.nz

UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

Pharyngeal pressure in healthy adults:
Comparison of unidirectional versus circumferential measures.

CONSENT FORM

I have been given a full explanation of this project and have been given an opportunity to ask questions. I understand what will be required of me if I agree to take part in this project. I understand that my participation is voluntary and that I may withdraw at any stage without penalty. Withdrawal of participation will also include the withdrawal of any information I have provided should this remain practically achievable.

I understand that any information or opinions I provide will be kept confidential to the researcher and that any published or reported results will not identify me. I understand that a thesis is a public document and will be available through the UC Library. I understand that all data collected for this study will be kept in locked and secure facilities at the New Zealand Brain Research Institute and will be destroyed after ten years.

I understand the risks associated with taking part and how they will be managed. I understand that I am able to receive a report on the findings of the study by contacting the researcher at the conclusion of the project. I understand that if I require further information I can contact the researcher, Kristin Lamvik, or her supervisor, Dr Maggie-Lee Huckabee. If I have any complaints about the research, I can contact the University of Canterbury Human Ethics Committee Private Bag 4800, Christchurch (human-ethics@canterbury.ac.nz).

By signing below, I agree to participate in this research project.

Date _____

Print Name of Participant _____

Signature of Participant _____

Date of Birth _____

Would you like to receive a summary of the research findings? (Choose one) Yes_____ No_____

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A copy of the information sheet has been provided to the participant.

Print Name of Researcher/person taking the consent _____

Signature of Researcher /person taking the consent _____

Date _____